

STIC Search Report

Biotech-Chem Library

STIC Database Tracking Number: 150423

TO: Shaojia A Jiang

Location: REM 4B09

Art Unit: 1617

April 11, 2005

Case Serial Number: 10/627160

From: P. Sheppard

Location: Remsen Building

Phone: (571) 272-2529

sheppard@uspto.gov

Search Notes

=> fil hcaplus
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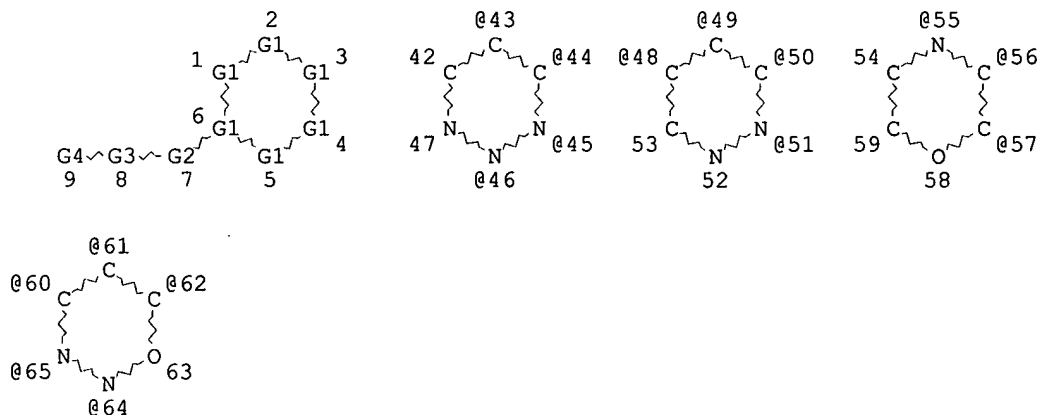
FILE COVERS 1907 - 11 Apr 2005 VOL 142 ISS 16
 FILE LAST UPDATED: 10 Apr 2005 (20050410/ED)

This file contains CAS Registry Numbers for easy and accurate substance identification.

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=> d stat que
 L1

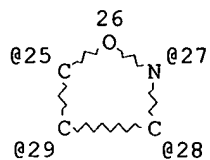
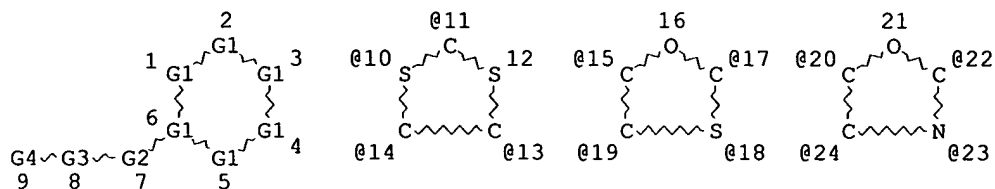
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 DEFAULT ECLEVEL IS LIMITED

GRAPH ATTRIBUTES:
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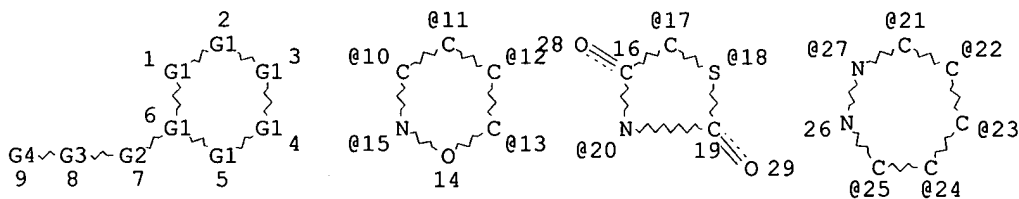
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GRAPH ATTRIBUTES:
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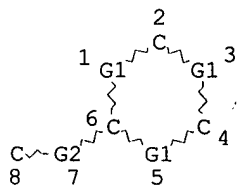
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 NODE ATTRIBUTES:
 DEFAULT MLEVEL IS ATOM
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GRAPH ATTRIBUTES:
 RING(S) ARE ISOLATED OR EMBEDDED
 NUMBER OF NODES IS 29

STEREO ATTRIBUTES: NONE
 L8 STR

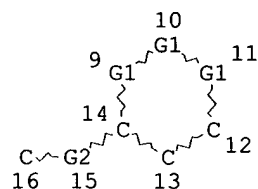


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GRAPH ATTRIBUTES:
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 NUMBER OF NODES IS 8

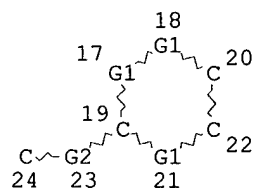
STEREO ATTRIBUTES: NONE
 L9 STR



VAR G1=C/N/O/S
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 NUMBER OF NODES IS 8

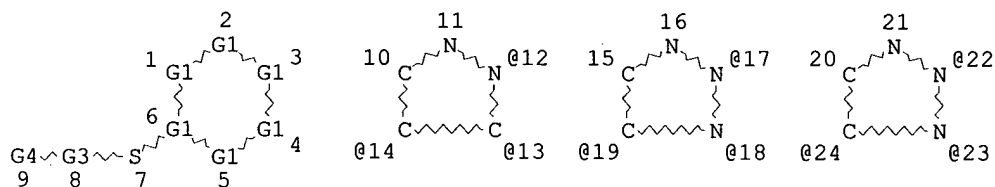
STEREO ATTRIBUTES: NONE
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 NUMBER OF NODES IS 8

STEREO ATTRIBUTES: NONE
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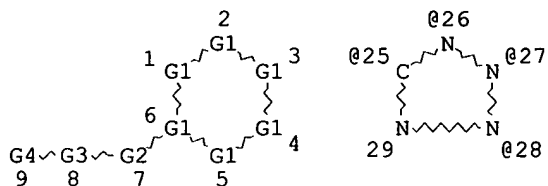


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GRAPH ATTRIBUTES:
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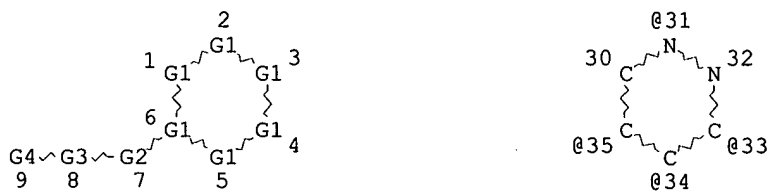
STEREO ATTRIBUTES: NONE
L37 STR



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DEFAULT ECLEVEL IS LIMITED

GRAPH ATTRIBUTES:
RING(S) ARE ISOLATED OR EMBEDDED
NUMBER OF NODES IS 14

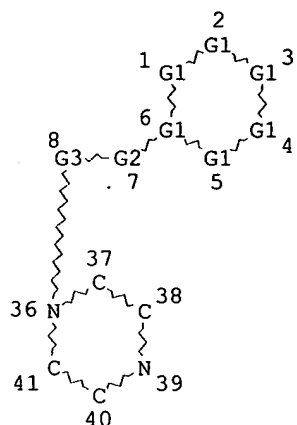
STEREO ATTRIBUTES: NONE
L42 STR



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VAR G2=O/S
REP G3=(1-15) C
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DEFAULT MLEVEL IS ATOM
DEFAULT ECLEVEL IS LIMITED

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RSPEC 30
NUMBER OF NODES IS 15

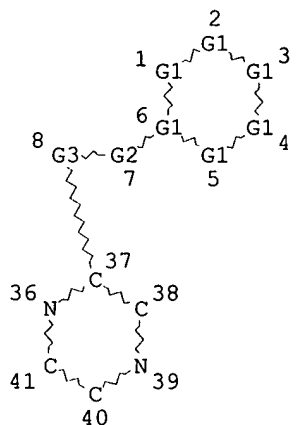
STEREO ATTRIBUTES: NONE
L46 STR



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VAR G2=O/S
REP G3=(1-15) C
NODE ATTRIBUTES:
DEFAULT MLEVEL IS ATOM
DEFAULT ECLEVEL IS LIMITED
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GRAPH ATTRIBUTES:
RSPEC 36
NUMBER OF NODES IS 14

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STEREO ATTRIBUTES: NONE
L51                STR
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VAR G1=C/N/O/S
VAR G2=O/S
REP G3=(1-15) C
NODE ATTRIBUTES:
DEFAULT MLEVEL IS ATOM
DEFAULT ECLEVEL IS LIMITED
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GRAPH ATTRIBUTES:
RSPEC 36
NUMBER OF NODES IS 14

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 L60 2264 SEA FILE=REGISTRY SSS FUL L37 AND (L8 OR L9 OR L10)
 L61 364 SEA FILE=REGISTRY SSS FUL L42 AND (L8 OR L9 OR L10)
 L62 37956 SEA FILE=REGISTRY SSS FUL L46 AND (L8 OR L9 OR L10)
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 L60 OR L61 OR L62 OR L63
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 .1/BI OR PPAR Γ 2/BI OR PPAR Γ 4/BI OR PPAR Γ E1/BI
 OR PPAR Γ FS/BI)
 L67 252 SEA FILE=REGISTRY ABB=ON PLU=ON PEROXISOME(L) PROLIFER?(L) RECE
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 L69 5023 SEA FILE=HCAPLUS ABB=ON PLU=ON (PEROXISOME(W) PROLIFER?(W) ACTI
 VAT?(5A) RECEPT? OR PPAR) (L) GAMMA
 L70 235 SEA FILE=HCAPLUS ABB=ON PLU=ON (L68 OR L69) AND L65
 L71 888 SEA FILE=HCAPLUS ABB=ON PLU=ON L65(L) (?NEOPLAS? OR ?CANCER?
 OR ?TUMOR? OR ?LEUKEM?)
 L72 14 SEA FILE=HCAPLUS ABB=ON PLU=ON L71 AND L70

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=>

=> d ibib abs hitstr 172 1-14

L72 ANSWER 1 OF 14 HCAPLUS COPYRIGHT 2005 ACS on STN

ACCESSION NUMBER: 2005:283359 HCAPLUS

TITLE: Medicinal composition

INVENTOR(S): Kawasugi, Kaname

PATENT ASSIGNEE(S): Japan

SOURCE: PCT Int. Appl., 14 pp.

CODEN: PIXXD2

DOCUMENT TYPE: Patent

LANGUAGE: Japanese

FAMILY ACC. NUM. COUNT: 1

PATENT INFORMATION:

| PATENT NO. | KIND | DATE | APPLICATION NO. | DATE |
|---|------|----------|-----------------|----------|
| WO 2005027967 | A1 | 20050331 | WO 2003-JP11847 | 20030917 |
| W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NI, NO, NZ, OM, PG, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, SY, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IT, LU, MC, NL, PT, RO, SE, SI, SK, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG | | | | |

PRIORITY APPLN. INFO.: WO 2003-JP11847 20030917

AB A medicinal composition which contains an insulin resistance-improving drug and
 vitamin B1 or its derivative In this medicinal composition, the side effects of
 the insulin resistance-improving drug of inducing edema, heart
 enlargement, anemia, etc. are prevented by using vitamin B1 or its derivative
 together. It is usable as a remedy for diabetes, a remedy for
 lifestyle-related diseases, an antitumor agent, an antirheumatoid drug and
 so on.

IT 250601-04-8, TAK 559

RL: DMA (Drug mechanism of action); THU (Therapeutic use); BIOL

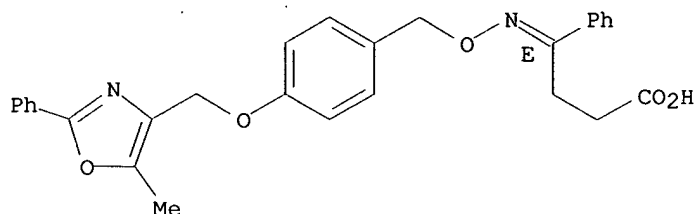
(Biological study); USES (Uses)

(PPAR γ agonist insulin resistance-improving

drugs and vitamin B1 or its derivs. as remedies for lifestyle-related

diseases, **antitumor** agents, antirheumatoid drugs, etc.)
 RN 250601-04-8 HCAPLUS
 CN Benzenebutanoic acid, γ -[[[4-[(5-methyl-2-phenyl-4-oxazolyl)methoxy]phenyl]methoxy]imino]-, (γ E)- (9CI) (CA INDEX NAME)

Double bond geometry as shown.



L72 ANSWER 2 OF 14 HCAPLUS COPYRIGHT 2005 ACS on STN

ACCESSION NUMBER: 2005:216621 HCAPLUS

DOCUMENT NUMBER: 142:291341

TITLE: Composition and method for the treatment of cancer and other physiologic conditions based on modulation of the **PPAR- γ** pathway and the HER kinase axis

INVENTOR(S): Agus, David B.; Jain, Anjali; Hedvat, Michael

PATENT ASSIGNEE(S): Cedars-Sinai Medical Center, USA

SOURCE: PCT Int. Appl., 43 pp.

CODEN: PIXXD2

DOCUMENT TYPE: Patent

LANGUAGE: English

FAMILY ACC. NUM. COUNT: 1

PATENT INFORMATION:

| PATENT NO. | KIND | DATE | APPLICATION NO. | DATE |
|---|------|----------|-----------------|----------|
| WO 2005020923 | A2 | 20050310 | WO 2004-US28071 | 20040827 |
| W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BW, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NA, NI, NO, NZ, OM, PG, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, SY, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW RW: BW, GH, GM, KE, LS, MW, MZ, NA, SD, SL, SZ, TZ, UG, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IT, LU, MC, NL, PL, PT, RO, SE, SI, SK, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG | | | | |

PRIORITY APPLN. INFO.: US 2003-498849P P 20030829
 US 2004-568910P P 20040507

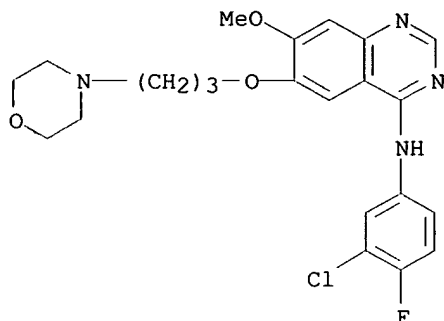
AB Methods are described for using a NSAID and a HER kinase axis inhibitor for the treatment of various conditions including cancer, and especially prostate, breast, lung, ovarian, brain and colon cancers, through regulation of **PPAR γ** activity. In various embodiments, the NSAID and HER kinase axis inhibitor may be included in a composition that is useful for the treatment of conditions in a mammal. Also described is a kit including a NSAID and a HER kinase axis inhibitor along with instructions for use in treating and preventing disease conditions, e.g. cancer.

IT 184475-35-2, Gefitinib

RL: PAC (Pharmacological activity); THU (Therapeutic use); BIOL (Biological study); USES (Uses)

(composition and method for treatment of **cancer** and other conditions based on modulation of **PPAR- γ** pathway and HER kinase axis)

RN 184475-35-2 HCAPLUS
 CN 4-Quinazolinamine, N-(3-chloro-4-fluorophenyl)-7-methoxy-6-[3-(4-morpholinyl)propoxy]- (9CI) (CA INDEX NAME)



L72 ANSWER 3 OF 14 HCAPLUS COPYRIGHT 2005 ACS on STN

ACCESSION NUMBER: 2004:964997 HCAPLUS

DOCUMENT NUMBER: 141:410816

TITLE: Preparation of azaheterocyclyl-substituted diphenylpyridines as Akt inhibitors for the treatment of cancer

INVENTOR(S): Bilodeau, Mark T.; Duggan, Mark E.; Hartnett, John C.; Lindsley, Craig W.; Wu, Zhicai; Zhao, Zhijian

PATENT ASSIGNEE(S): Merck & Co., Inc., USA

SOURCE: PCT Int. Appl., 98 pp.

CODEN: PIXXD2

DOCUMENT TYPE: Patent

LANGUAGE: English

FAMILY ACC. NUM. COUNT: 1

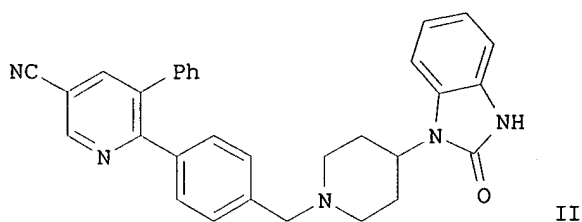
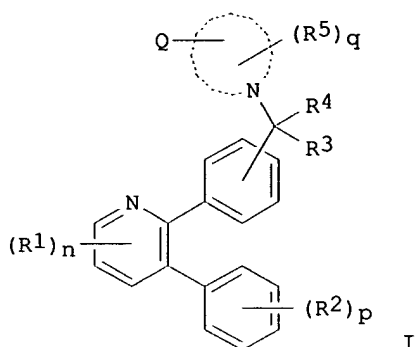
PATENT INFORMATION:

| PATENT NO. | KIND | DATE | APPLICATION NO. | DATE |
|---|------|----------|-----------------|----------|
| WO 2004096131 | A2 | 20041111 | WO 2004-US12188 | 20040420 |
| W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BW, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NA, NI, NO, NZ, OM, PG, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, SY, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW | | | | |
| RW: BW, GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IT, LU, MC, NL, PL, PT, RO, SE, SI, SK, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG | | | | |

PRIORITY APPLN. INFO.: US 2003-465260P P 20030424

OTHER SOURCE(S): MARPAT 141:410816

GI



AB Azaheterocyclyl-substituted diphenylpyridines I [uppermost nitrogen-containing ring is a heterocycle; R1, R2, R5 = (un)substituted alkyl, aryl, heteroaryl, alkenyl, alkynyl, HO2C, NC, halo, HO, OHC, O2N, alkoxy, etc.; R3, R4 = H, alkyl, perfluoroalkyl; R3, R4, and the carbon to which they are bonded may form a carbocycle or a heterocycle containing O, S, S(:O), SO2, (un)substituted N or NHC(:O); n = 0-3; p = 0-2; q = 0-3] such as II are prepared as inhibitors of Akt1, Akt2, or Akt3 for the treatment of cancer alone or in conjunction with other drugs or radiation therapy. Trifluorosulfonylation of 6-hydroxy-5-phenyl-3-pyridinecarbonitrile, palladium-catalyzed Suzuki coupling with 4-formylphenylboronic acid, and reductive amination of the aldehyde with 1-(4-piperidinyl)-2,3-dihydro-2-benzimidazolone yields II as its TFA salt. I inhibit one or more of Akt1, Akt2, or Akt3 with IC50 values of $\leq 50 \mu\text{M}$ (no data).

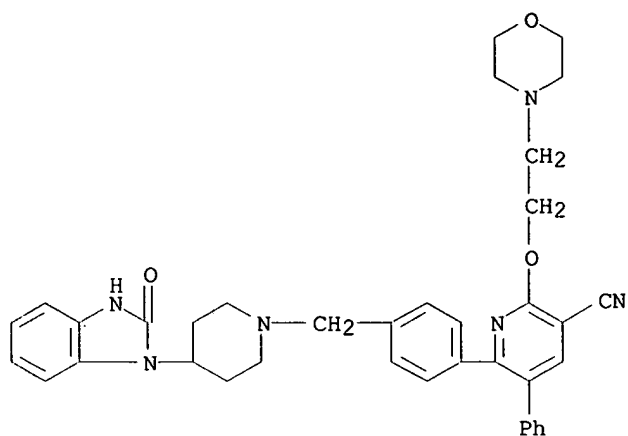
IT **791851-43-9P 791852-14-7P**

RL: PAC (Pharmacological activity); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)

(invention compound; preparation of azaheterocyclyl-substituted diphenylpyridines as Akt inhibitors for the treatment of **cancer**

RN 791851-43-9 HCAPLUS

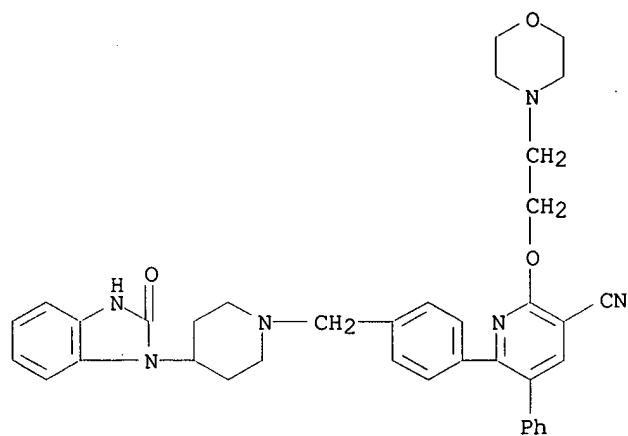
CN 3-Pyridinecarbonitrile, 6-[4-[[4-(2,3-dihydro-2-oxo-1H-benzimidazol-1-yl)-1-piperidinyl]methyl]phenyl]-2-[2-(4-morpholinyl)ethoxy]-5-phenyl- (9CI) (CA INDEX NAME)



RN 791852-14-7 HCAPLUS
 CN 3-Pyridinecarbonitrile, 6-[4-[[4-(2,3-dihydro-2-oxo-1H-benzimidazol-1-yl)-1-piperidinyl]methyl]phenyl]-2-[2-(4-morpholinyl)ethoxy]-5-phenyl-, trifluoroacetate (9CI) (CA INDEX NAME)

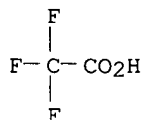
CM 1

CRN 791851-43-9
 CMF C37 H38 N6 O3



CM 2

CRN 76-05-1
 CMF C2 H F3 O2



ACCESSION NUMBER: 2004:433750 HCAPLUS
 DOCUMENT NUMBER: 141:7131
 TITLE: Preparation of quinazolines and analogs as Akt inhibitors and indoles as protein kinase inhibitors for use in synergistic combination therapy for the treatment of cancer
 INVENTOR(S): Barnett, Stanley F.; Defeo-Jones, Deborah D.; Hartman, George D.; Huber, Hans E.; Stirdivant, Steven M.; Heimbrosk, David C.
 PATENT ASSIGNEE(S): USA
 SOURCE: U.S. Pat. Appl. Publ., 121 pp., which CODEN: USXXCO
 DOCUMENT TYPE: Patent
 LANGUAGE: English
 FAMILY ACC. NUM. COUNT: 1
 PATENT INFORMATION:

| PATENT NO. | KIND | DATE | APPLICATION NO. | DATE |
|------------------------|------|----------|-----------------|------------|
| US 2004102360 | A1 | 20040527 | US 2003-678565 | 20031003 |
| PRIORITY APPLN. INFO.: | | | US 2002-422312P | P 20021030 |
| | | | US 2003-460911P | P 20030407 |

OTHER SOURCE(S): MARPAT 141:7131
 GI

* STRUCTURE DIAGRAM TOO LARGE FOR DISPLAY - AVAILABLE VIA OFFLINE PRINT *

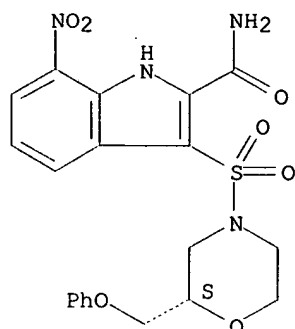
AB The present invention relates to methods of treating cancer using a combination of at least two Akt inhibitors I [wherein Q = (un)substituted heterocyclyl, aryl; U, V, W, and X = independently CH, N; Y, Z = independently CH, N, provided that at least one of Y and Z = N; n = 0-3; p = 0-2; q = 0-4; R1, R2, R7 = independently halo, CN, OH, CHO, NO2, or (un)substituted (cyclo)alkyl(oxy), alkenyl(oxy), alkynyl(oxy), heterocyclyl(oxy), acyl, carboxy, carbamoyl(oxy), ureido, sulfamoyl, etc.; R3, R4 = independently H, (perfluoro)alkyl; or CR3R4 = cycloalkyl, heterocyclyl; and pharmaceutically acceptable salts or stereoisomers thereof] or a combination of I and a protein kinase inhibitor II [wherein G = H2, O; X = C, N, SO0-2, O; m = 0-2; n = 0-2; p = 0-6; q = 0-4; R1 = independently H, halo, or (un)substituted (cyclo)alkyl, heterocyclyl, aryl, carbamoyl, amino, acyl, sulfamoyl, carboxy, etc.; R2 = H or (un)substituted (cyclo)alkyl(oxy), amino, aryloxy, heterocycliloxy, alkenyloxy, alkynyloxy, etc.; R5 = independently H, halo, NO2, CN, or (un)substituted alkyl, alkenyl, alkynyl, carboxy, acyl, sulfamoyl, carbamoyl, ureido, amino, etc.; and pharmaceutically acceptable salts or stereoisomers thereof], optionally in combination with a third compound. Examples include syntheses for I and II and assays demonstrating Akt inhibitor activity, antitumor activity, and the synergistic effect of combinations of AKT inhibitors and/or protein kinase inhibitors on caspase 3 activity. For instance, III•HCl was prepared in an 8-step reaction sequence culminating with the cycloaddn. of 4-(2-aminoprop-2-yl)benzil and o-phenylenediamine using glacial acetic acid in H2O, followed by work up with chloroform and ethanolic HCl. III•HCl, a selective Akt1 and Akt2 inhibitor, demonstrated a 3.2-fold in caspase 3 activation over control compared to a 1.2-fold increase for a protein kinase inhibitor. Combination treatment produced a 9-fold increase in caspase 3 activation.

IT **661468-61-7P 661468-63-9P**
 RL: PAC (Pharmacological activity); RCT (Reactant); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); RACT (Reactant or reagent); USES (Uses)
 (antitumor agent; preparation of quinazolines and analogs as Akt inhibitors and indoles as protein kinase inhibitors for use in synergistic combination therapy for treatment of cancer)

RN 661468-61-7 HCAPLUS

CN 1H-Indole-2-carboxamide, 7-nitro-3-[[(2S)-2-(phoxymethyl)-4-morpholinyl]sulfonyl]- (9CI) (CA INDEX NAME)

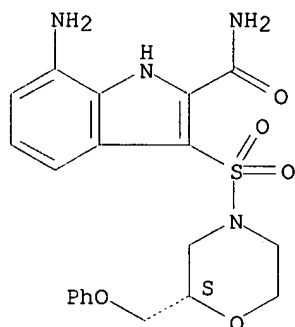
Absolute stereochemistry.



RN 661468-63-9 HCAPLUS

CN 1H-Indole-2-carboxamide, 7-amino-3-[[(2S)-2-(phoxymethyl)-4-morpholinyl]sulfonyl]- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



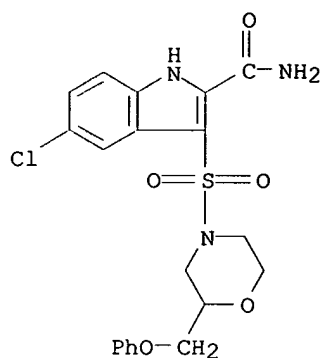
IT 661467-97-6P 661467-98-7P 661467-99-8P
661468-12-8P 661468-13-9P 661468-14-0P
661468-53-7P 661468-54-8P 661468-55-9P
661468-65-1P 661468-67-3P 661468-75-3P
661468-76-4P 661468-87-7P 661469-61-0P
661469-89-2P 661470-00-4P

RL: PAC (Pharmacological activity); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)

(antitumor agent; preparation of quinazolines and analogs as Akt inhibitors and indoles as protein kinase inhibitors for use in synergistic combination therapy for treatment of cancer)

RN 661467-97-6 HCAPLUS

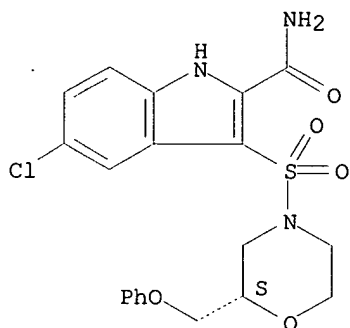
CN 1H-Indole-2-carboxamide, 5-chloro-3-[[2-(phoxymethyl)-4-morpholinyl]sulfonyl]- (9CI) (CA INDEX NAME)



RN 661467-98-7 HCAPLUS

CN 1H-Indole-2-carboxamide, 5-chloro-3-[[2-(phenoxy)methyl]-4-morpholinyl]sulfonyl- (9CI) (CA INDEX NAME)

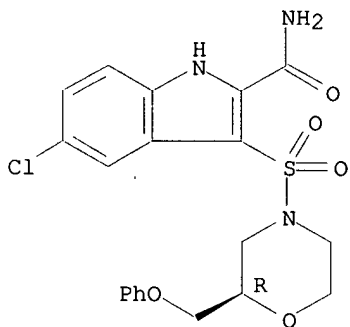
Absolute stereochemistry.



RN 661467-99-8 HCAPLUS

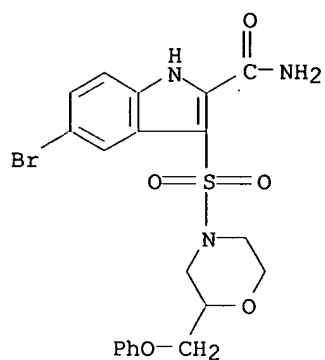
CN 1H-Indole-2-carboxamide, 5-chloro-3-[[2-(phenoxy)methyl]-4-morpholinyl]sulfonyl- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



RN 661468-12-8 HCAPLUS

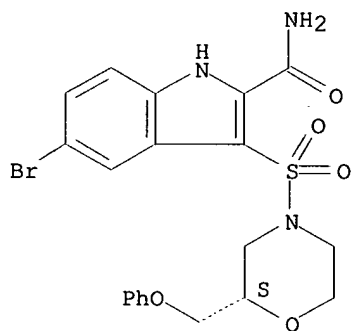
CN 1H-Indole-2-carboxamide, 5-bromo-3-[[2-(phenoxy)methyl]-4-morpholinyl]sulfonyl- (9CI) (CA INDEX NAME)



RN 661468-13-9 HCAPLUS

CN 1H-Indole-2-carboxamide, 5-bromo-3-[[2-(phoxymethyl)-4-morpholinyl]sulfonyl]- (9CI) (CA INDEX NAME)

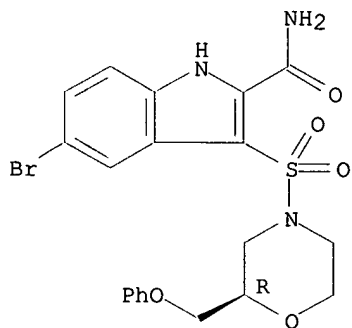
Absolute stereochemistry.



RN 661468-14-0 HCAPLUS

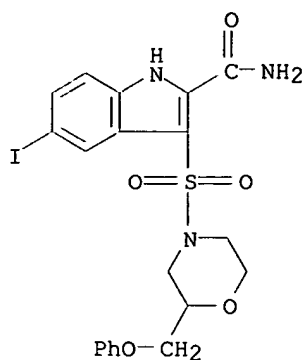
CN 1H-Indole-2-carboxamide, 5-bromo-3-[[2R)-2-(phoxymethyl)-4-morpholinyl]sulfonyl]- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



RN 661468-53-7 HCAPLUS

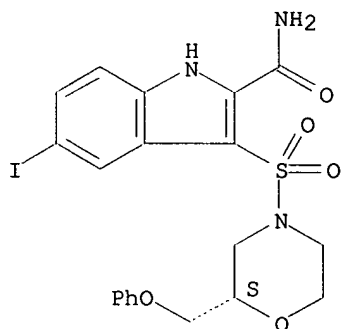
CN 1H-Indole-2-carboxamide, 5-iodo-3-[[2-(phoxymethyl)-4-morpholinyl]sulfonyl]- (9CI) (CA INDEX NAME)



RN 661468-54-8 HCAPLUS

CN 1H-Indole-2-carboxamide, 5-iodo-3-[[2-(phenoxy)methyl]-4-morpholinyl]sulfonyl- (9CI) (CA INDEX NAME)

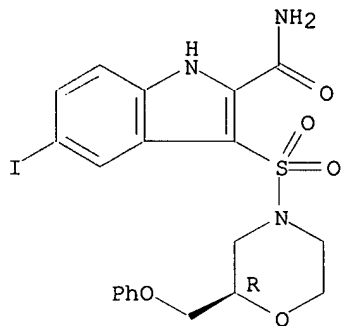
Absolute stereochemistry.



RN 661468-55-9 HCAPLUS

CN 1H-Indole-2-carboxamide, 5-iodo-3-[[2R]-2-(phenoxy)methyl]-4-morpholinyl]sulfonyl- (9CI) (CA INDEX NAME)

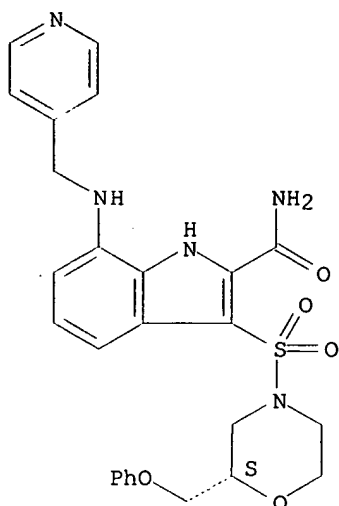
Absolute stereochemistry.



RN 661468-65-1 HCAPLUS

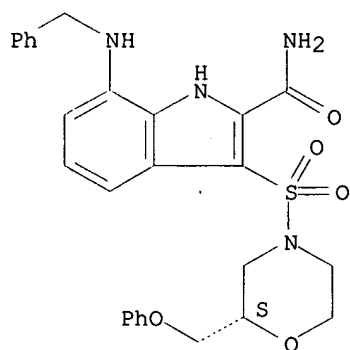
CN 1H-Indole-2-carboxamide, 3-[[2S]-2-(phenoxy)methyl]-4-morpholinyl]sulfonyl]-7-[(4-pyridinylmethyl)amino]- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



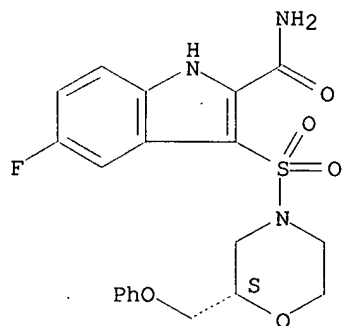
RN 661468-67-3 HCAPLUS
 CN 1H-Indole-2-carboxamide, 3-[[(2S)-2-(phenoxymethyl)-4-morpholinyl]sulfonyl]-7-[(phenylmethyl)amino]- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



RN 661468-75-3 HCAPLUS
 CN 1H-Indole-2-carboxamide, 5-fluoro-3-[[(2S)-2-(phenoxymethyl)-4-morpholinyl]sulfonyl]- (9CI) (CA INDEX NAME)

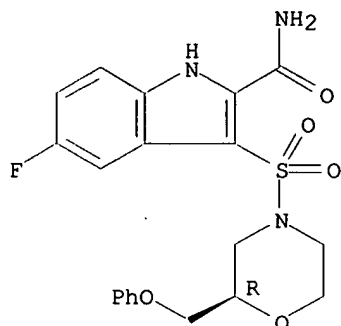
Absolute stereochemistry.



RN 661468-76-4 HCAPLUS

CN 1H-Indole-2-carboxamide, 5-fluoro-3-[[(2R)-2-(phenoxyethyl)-4-morpholinyl]sulfonyl]- (9CI) (CA INDEX NAME)

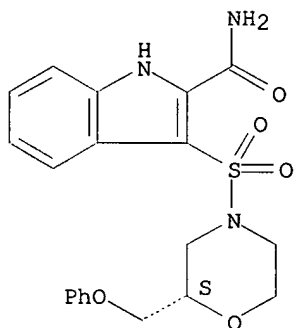
Absolute stereochemistry.



RN 661468-87-7 HCAPLUS

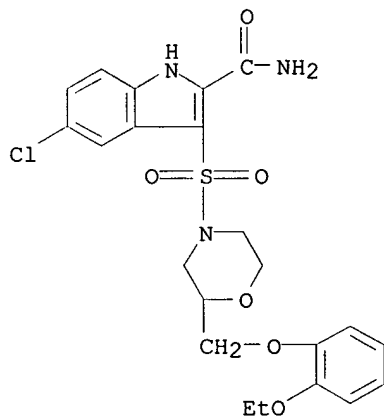
CN 1H-Indole-2-carboxamide, 3-[[(2S)-2-(phenoxyethyl)-4-morpholinyl]sulfonyl]- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



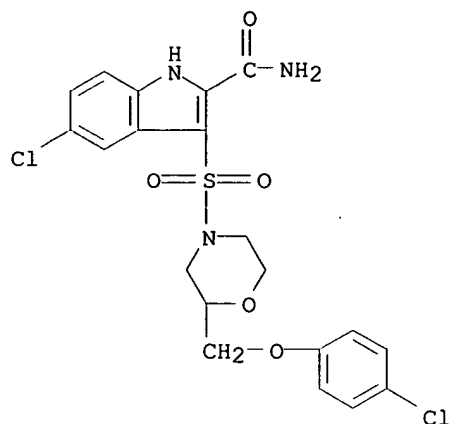
RN 661469-61-0 HCAPLUS

CN 1H-Indole-2-carboxamide, 5-chloro-3-[[2-[(2-ethoxyphenoxy)methyl]-4-morpholinyl]sulfonyl]- (9CI) (CA INDEX NAME)



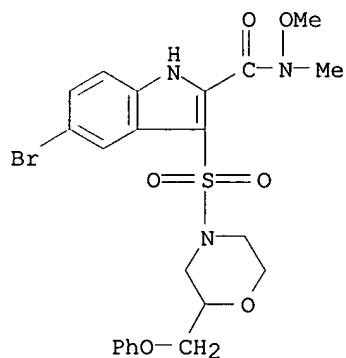
RN 661469-89-2 HCAPLUS

CN 1H-Indole-2-carboxamide, 5-chloro-3-[[2-[(4-chlorophenoxy)methyl]-4-morpholinyl]sulfonyl]- (9CI) (CA INDEX NAME)



RN 661470-00-4 HCAPLUS

CN 1H-Indole-2-carboxamide, 5-bromo-N-methoxy-N-methyl-3-[[2-(phenoxy)methyl]-4-morpholinyl]sulfonyl]- (9CI) (CA INDEX NAME)



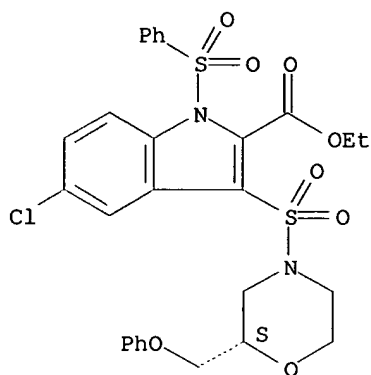
IT 661470-45-7P 695816-07-0P

RL: RCT (Reactant); SPN (Synthetic preparation); PREP (Preparation); RACT (Reactant or reagent)
(intermediate; preparation of quinazolines and analogs as Akt inhibitors and indoles as protein kinase inhibitors for use in synergistic combination therapy for treatment of **cancer**)

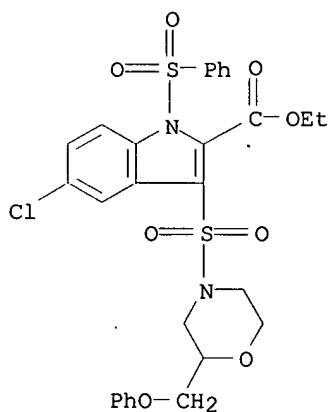
RN 661470-45-7 HCAPLUS

CN 1H-Indole-2-carboxylic acid, 5-chloro-3-[[2-(phenoxy)methyl]-4-morpholinyl]sulfonyl]-1-(phenylsulfonyl)-, ethyl ester (9CI) (CA INDEX NAME)

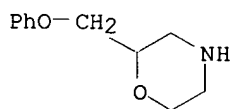
Absolute stereochemistry.



RN 695816-07-0 HCAPLUS
 CN 1H-Indole-2-carboxylic acid, 5-chloro-3-[[2-(phenoxyethyl)-4-morpholinyl]sulfonyl]-1-(phenylsulfonyl)-, ethyl ester (9CI) (CA INDEX NAME)

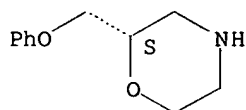


IT 167273-56-5, 2-(Phenoxyethyl)morpholine 661470-52-6
 695816-08-1 695816-09-2
 RL: RCT (Reactant); RACT (Reactant or reagent)
 (preparation of quinazolines and analogs as Akt inhibitors and indoles as protein kinase inhibitors for use in synergistic combination therapy for treatment of **cancer**)
 RN 167273-56-5 HCAPLUS
 CN Morpholine, 2-(phenoxyethyl)- (9CI) (CA INDEX NAME)



RN 661470-52-6 HCAPLUS
 CN Morpholine, 2-(phenoxyethyl)-, (2S)- (9CI) (CA INDEX NAME)

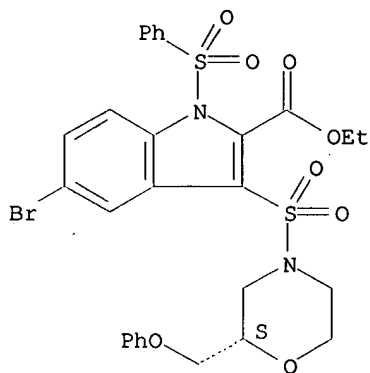
Absolute stereochemistry.



RN 695816-08-1 HCAPLUS

CN 1H-Indole-2-carboxylic acid, 5-bromo-3-[[[(2S)-2-(phenoxy)methyl]-4-morpholinyl]sulfonyl]-1-(phenylsulfonyl)-, ethyl ester (9CI) (CA INDEX NAME)

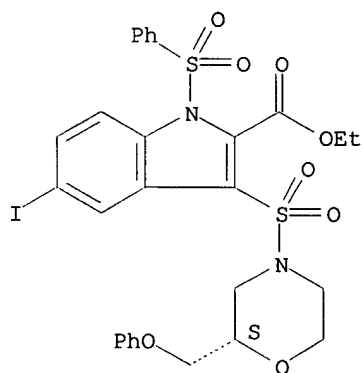
Absolute stereochemistry.



RN 695816-09-2 HCAPLUS

CN 1H-Indole-2-carboxylic acid, 5-iodo-3-[[[(2S)-2-(phenoxy)methyl]-4-morpholinyl]sulfonyl]-1-(phenylsulfonyl)-, ethyl ester (9CI) (CA INDEX NAME)

Absolute stereochemistry.



L72 ANSWER 5 OF 14 HCAPLUS COPYRIGHT 2005 ACS on STN

ACCESSION NUMBER: 2004:120834 HCAPLUS

DOCUMENT NUMBER: 140:181466

TITLE: Preparation of resorcinol derivatives as
**peroxisome proliferator-
 activated receptor (PPAR)**
 γ-agonists

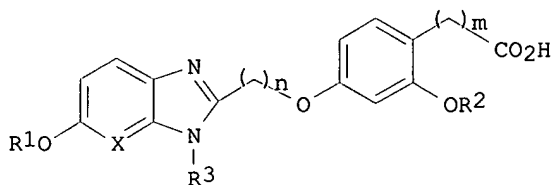
INVENTOR(S): Shibata, Tomoyuki; Wada, Kunio; Nakamura, Yuji; Araki,
 Kazushi

PATENT ASSIGNEE(S): Sankyo Company, Limited, Japan

SOURCE: PCT Int. Appl., 261 pp.
 CODEN: PIXXD2
 DOCUMENT TYPE: Patent
 LANGUAGE: Japanese
 FAMILY ACC. NUM. COUNT: 1
 PATENT INFORMATION:

| PATENT NO. | KIND | DATE | APPLICATION NO. | DATE |
|---|------|----------|-------------------|------------|
| WO 2004013109 | A1 | 20040212 | WO 2003-JP9834 | 20030801 |
| W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NI, NO, NZ, OM, PG, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, SY, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IT, LU, MC, NL, PT, RO, SE, SI, SK, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG | | | | |
| JP 2004123711 | A2 | 20040422 | JP 2003-205222 | 20030801 |
| PRIORITY APPLN. INFO.: | | | JP 2002-225980 | A 20020802 |
| OTHER SOURCE(S): | | | MARPAT 140:181466 | |

GI



AB 4-[(Pyrido[2,3-d]imidazol-2-yl or benzimidazol-2-ylalkoxy)phenyl]propanoic acid or acetic acid derivs. represented by the following general formula (I) [wherein X = CH, N; R1 = each (un)substituted C1-6 alkyl, C3-10 cycloalkyl, C2-6 alkenyl, C6-10 aryl, C7-16 aralkyl, 4- to 10-membered heterocycle containing one to three heteroatoms selected from N, O, and S atoms; R2 = each (un)substituted C7-16 aralkyl, C9-16 aralkenyl, or alkyl substituted by a 5- to 10-membered heteroarom. ring containing one to three heteroatoms selected from N, O, and S atoms; R3 = H, C1-6 alkyl, (un)substituted C6-10 aryl; m = 1, 2; n = an integer of 1-3] or pharmacol. acceptable salts or esters thereof are prepared. Also disclosed are pharmaceutical compns. containing the compds. I or pharmacol. acceptable salts or esters thereof as the active ingredients (1) for improving insulin-resistance, lowering blood sugar, or inhibiting the proliferation of cancer cells or (2) for the prevention and/or treatment of diabetes, impaired glucose tolerance, obesity, hyperlipemia, or diabetes complications. Thus, 1.09 g 3-(2-benzyloxy-4-hydroxyphenyl)propionic acid Et ester and 697 mg 2-hydroxymethyl-6-methoxy-1-methyl-1H-benzimidazole were dissolved in 30 mL toluene, treated with 1.13 mL tributylphosphine and 1.14 g 1,1'-(azodicarbonyl)dipiperidine and stirred at room temperature overnight to give 87% 3-[2-benzyloxy-4-(6-methoxy-1-methyl-1H-benzimidazol-2-ylmethoxy)phenyl]propionic acid Et ester which (1.5 g) was stirred with a mixture of 7 mL EtOH, 7 mL THF, and 6.3 mL 1 N aqueous NaOH at room temperature overnight and stirred with 1 N aqueous HCl and EtOAc to give 45% 3-[2-benzyloxy-4-(6-methoxy-1-methyl-1H-benzimidazol-2-ylmethoxy)phenyl]propionic acid (II). 3-[4-[2-[6-(4-Amino-3,5-dimethylphenoxy)-1-methyl-1H-benzimidazol-2-yl]ethoxy]-2-(4-chlorobenzyloxy)phenyl]propionic acid hydrochloride was fed to male KK mice with a feed containing 0.01% II for 3 days to lower blood sugar level by 71%.

A capsule, a tablet, and a granule containing I were formulated.

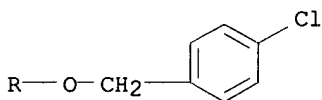
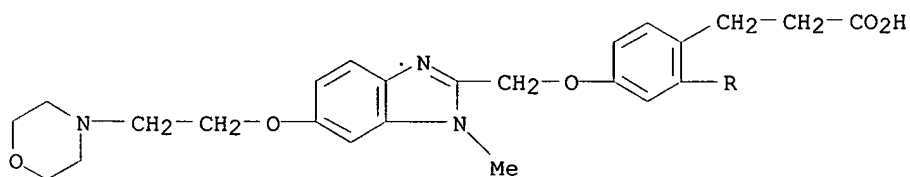
IT 657429-91-9P

RL: PAC (Pharmacological activity); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)

(preparation of resorcinol derivs. as **peroxisome proliferator-activated receptor (PPAR)** γ -agonists, anticancer agents, or treatment or prevention of diabetes, impaired glucose tolerance, obesity, or hyperlipemia)

RN 657429-91-9 HCAPLUS

CN Benzenepropanoic acid, 2-[(4-chlorophenyl)methoxy]-4-[[1-methyl-6-[2-(4-morpholinyl)ethoxy]-1H-benzimidazol-2-yl]methoxy]-, dihydrochloride (9CI) (CA INDEX NAME)



● 2 HCl

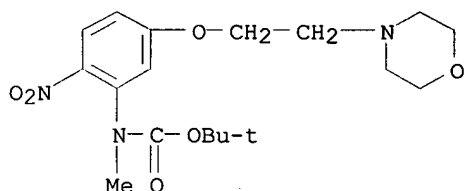
IT 657431-74-8P 657431-75-9P 657431-76-0P
657431-77-1P

RL: RCT (Reactant); SPN (Synthetic preparation); PREP (Preparation); RACT (Reactant or reagent)

(preparation of resorcinol derivs. as **peroxisome proliferator-activated receptor (PPAR)** γ -agonists, anticancer agents, or treatment or prevention of diabetes, impaired glucose tolerance, obesity, or hyperlipemia)

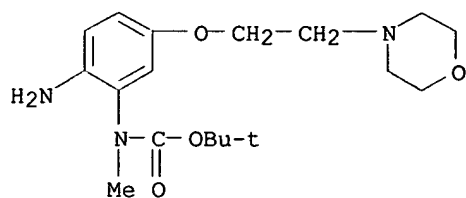
RN 657431-74-8 HCAPLUS

CN Carbamic acid, methyl[5-[2-(4-morpholinyl)ethoxy]-2-nitrophenyl]-, 1,1-dimethylethyl ester (9CI) (CA INDEX NAME)



RN 657431-75-9 HCAPLUS

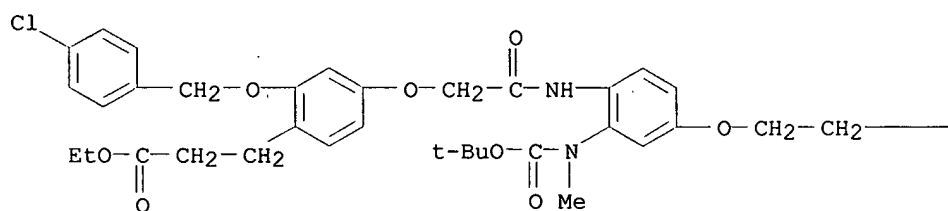
CN Carbamic acid, [2-amino-5-[2-(4-morpholinyl)ethoxy]phenyl]methyl-, 1,1-dimethylethyl ester (9CI) (CA INDEX NAME)



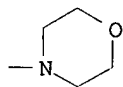
RN 657431-76-0 HCAPLUS

CN Benzenepropanoic acid, 2-[(4-chlorophenyl)methoxy]-4-[2-[[2-[(1,1-dimethylethoxy)carbonyl]methylamino]-4-[2-(4-morpholinyl)ethoxy]phenyl]amino]-2-oxoethoxy]-, ethyl ester (9CI) (CA INDEX NAME)

PAGE 1-A



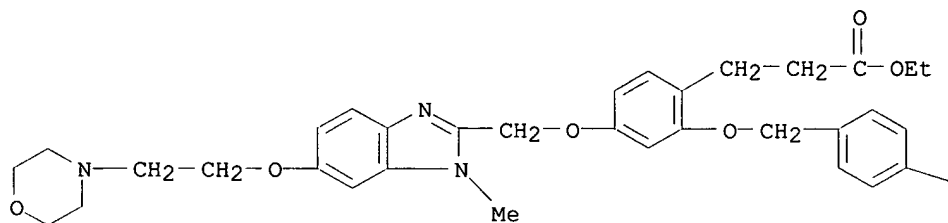
PAGE 1-B



RN 657431-77-1 HCAPLUS

CN Benzenepropanoic acid, 2-[(4-chlorophenyl)methoxy]-4-[[1-methyl-6-[2-(4-morpholinyl)ethoxy]-1H-benzimidazol-2-yl]methoxy]-, ethyl ester (9CI) (CA INDEX NAME)

PAGE 1-A

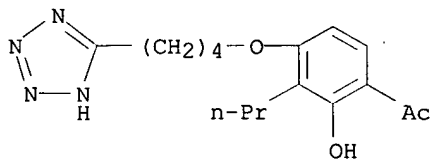


c1

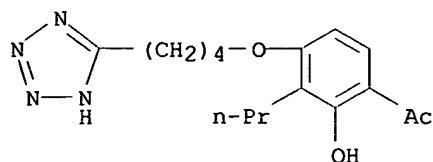
L72 ANSWER 6 OF 14 HCAPLUS COPYRIGHT 2005 ACS on STN
 ACCESSION NUMBER: 2003:334376 HCAPLUS
 DOCUMENT NUMBER: 138:362646
 TITLE: Use of lipoxygenase inhibitors and PPAR ligands as anticancer therapeutic and intervention agents
 INVENTOR(S): Mulshine, James L.; Jett, Marti
 PATENT ASSIGNEE(S): The United States of America as Represented by the Department of Health and Human Services, USA; The United States of America as Represented by the Secretary of the Army
 SOURCE: U.S. Pat. Appl. Publ., 12 pp.
 CODEN: USXXCO
 DOCUMENT TYPE: Patent
 LANGUAGE: English
 FAMILY ACC. NUM. COUNT: 1
 PATENT INFORMATION:

| PATENT NO. | KIND | DATE | APPLICATION NO. | DATE |
|---------------|------|----------|-----------------|----------|
| US 2003082108 | A1 | 20030501 | US 2002-186070 | 20020628 |
| US 6756399 | B2 | 20040629 | | |

PRIORITY APPLN. INFO.: US 2001-302155P P 20010629
 AB The invention provides a method for treating and preventing an epithelial cell-derived cancer in a subject in need thereof, comprising administering to the subject an amount of a 5-lipoxygenase inhibitor and PPAR ligand or derivs. thereof, effective to treat or prevent the epithelial cell-derived cancer. Also encompassed by the invention are inhibitors of enzymes that metabolize arachidonic acid.
 IT 88107-10-2, LY171883 88107-10-2D, LY171883, derivs.
 RL: PAC (Pharmacological activity); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
 (lipoxygenase inhibitors and PPAR ligands as **anticancer** therapeutic and intervention agents)
 RN 88107-10-2 HCAPLUS
 CN Ethanone, 1-[2-hydroxy-3-propyl-4-[4-(1H-tetrazol-5-yl)butoxy]phenyl]-(9CI) (CA INDEX NAME)



RN 88107-10-2 HCAPLUS
 CN Ethanone, 1-[2-hydroxy-3-propyl-4-[4-(1H-tetrazol-5-yl)butoxy]phenyl]-(9CI) (CA INDEX NAME)



REFERENCE COUNT: 14 THERE ARE 14 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L72 ANSWER 7 OF 14 HCAPLUS COPYRIGHT 2005 ACS on STN

ACCESSION NUMBER: 2003:297161 HCAPLUS

DOCUMENT NUMBER: 139:148276

TITLE: **PPAR γ** Ligands and ATRA Inhibit the Invasion of Human Breast Cancer Cells in vitro

AUTHOR(S): Liu, H.; Zang, C.; Fenner, M. H.; Possinger, K.; Elstner, E.

CORPORATE SOURCE: School of Medicine (Charite), Humboldt University, Berlin, Germany

SOURCE: Breast Cancer Research and Treatment (2003), 79(1), 63-74

CODEN: BCTRD6; ISSN: 0167-6806

PUBLISHER: Kluwer Academic Publishers

DOCUMENT TYPE: Journal

LANGUAGE: English

AB Invasion and metastasis are the main causes of death in breast cancer patients. Increased expression of matrix metalloproteinases (MMPs), especially gelatinases (MMP-2 and -9), has been closely associated with tumor progression. One of the nuclear hormone **receptors** (NHR), **peroxisome proliferator-activated receptor γ (PPAR γ)**, is a ligand-activated transcriptional factor that regulates cell proliferation, differentiation and apoptosis in both normal and cancer cells. Recent data indicate that **PPAR γ** activation by its ligands can also lead to the inhibition of gelatinase B (MMP-9) and the blockage of migration in macrophages and muscle cells, implying the possibility that **PPAR γ** ligands may possess anti-invasive activities on tumor cells. In this study, we showed that treatment of the highly aggressive human breast cancer cell line MDA-MB-231 with the synthetic **PPAR γ** ligands pioglitazone (PGZ), rosiglitazone (RGZ), GW7845 or its natural ligand 15-deoxy- Δ 12, 14-prostaglandin J2 (15d-PGJ2), at concns. at which no obvious cytotoxicity was observed in vitro, led to a significant inhibition of the invasive capacities of this cell line through a reconstituted basement membrane (Matrigel) in a Transwell chamber model. All-trans-retinoic acid (ATRA), a ligand for retinoic acid receptor (RAR), was also studied and showed a similar inhibitory effect on invasion. Although no change was observed in the expression of MMP-9 after challenge with **PPAR γ** ligands and/or ATRA on this cell line, the natural tissue inhibitor of gelatinases, namely the tissue inhibitor of MMP 1 (TIMP-1) was upregulated by these treatments and the gelatinolytic activities of gelatinases in the conditioned media were decreased. Since MMP-2 was not detectable in the conditioned media of MDA-MB-231 cells, and the gelatinolytic activities of the conditioned media were reduced only by MMP-9 neutralizing antibodies, it is most likely that the reduction of gelatinolytic activities by **PPAR γ** ligands and/or ATRA was due to the decrease of MMP-9 activities. Because MMP-9 was absolutely required in the transmigration of this cell line through Matrigel in our in vitro model as demonstrated by neutralizing antibodies against MMP-2 and -9, we concluded that down-regulation of gelatinase activities is, at least in part, responsible for the reduction of the invasive capacities of MDA-MB-231 cell line in vitro. Our results, for the first time, indicate that **PPAR γ** .

gamma. ligands may have therapeutic value for the treatment of highly invasive breast cancer by targeting its invasive behavior.

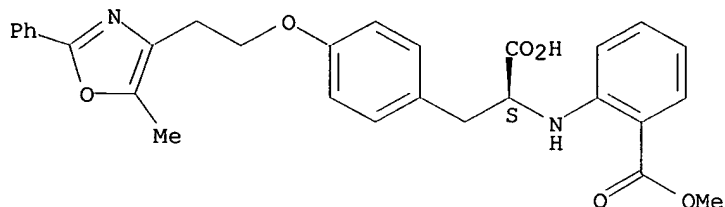
IT 196809-22-0, GW 7845

RL: BSU (Biological study, unclassified); BIOL (Biological study)
(PPARY ligands and ATRA inhibit the invasion
of human breast cancer cells in vitro)

RN 196809-22-0 HCAPLUS

CN L-Tyrosine, N-[2-(methoxycarbonyl)phenyl]-O-[2-(5-methyl-2-phenyl-4-oxazolyl)ethyl]- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



REFERENCE COUNT: 24 THERE ARE 24 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L72 ANSWER 8 OF 14 HCAPLUS COPYRIGHT 2005 ACS on STN

ACCESSION NUMBER: 2003:202621 HCAPLUS

DOCUMENT NUMBER: 138:238027

TITLE: Preparation of 3-(2-indolyl)quinolin-2(1H)-ones as tyrosine kinase inhibitors

INVENTOR(S): Peckham, Jennifer P.; Hoffman, William F.; Arrington, Kenneth L.; Fraley, Mark E.; Hartman, George D.; Kim, Yuntae; Hanney, Barbara; Spencer, Keith L.

PATENT ASSIGNEE(S): Merck & Co., Inc., USA

SOURCE: PCT Int. Appl., 143 pp.

CODEN: PIXXD2

DOCUMENT TYPE: Patent

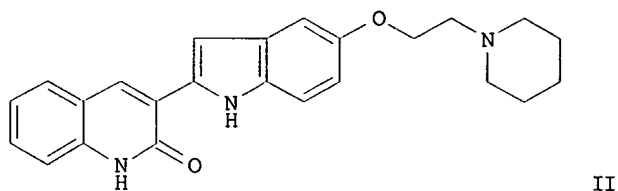
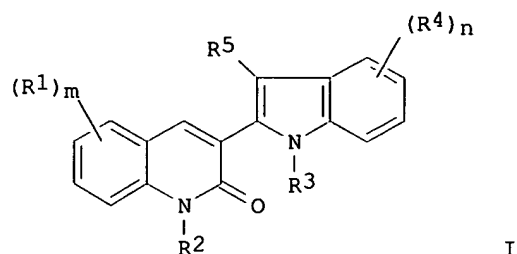
LANGUAGE: English

FAMILY ACC. NUM. COUNT: 1

PATENT INFORMATION:

| PATENT NO. | KIND | DATE | APPLICATION NO. | DATE |
|---|------|----------|-----------------|------------|
| WO 2003020699 | A2 | 20030313 | WO 2002-US27114 | 20020826 |
| WO 2003020699 | A3 | 20030522 | | |
| W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, OM, PH, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW | | | | |
| RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, SK, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG | | | | |
| US 2004235826 | A1 | 20041125 | US 2004-487589 | 20040224 |
| PRIORITY APPLN. INFO.: | | | US 2001-316123P | P 20010830 |
| | | | WO 2002-US27114 | W 20020826 |

GI



AB Title compds., including I (R groups undefined), were prepared and inhibitors, regulators, and/or modulators of tyrosine kinase signal transduction. For example, 1-(tert-butoxycarbonyl)-5-[(tert-butyldimethylsilyl)oxy]-1H-indol-2-ylboronic acid was coupled with 2-chloro-3-iodoquinoline (preparation of starting materials given) in the presence of Pd(PPh₃)₄ and K₃PO₄ in dioxane to give the protected 3-(2-indolyl)quinoline derivative. Deprotection using triethylamine trihydrofluoride afforded the alc. Reaction with 1-(2-chloroethyl)piperidine•HCl and Cs₂CO₃ in DMF followed by reflux at 110° in AcOH and H₂O for 12 h provided II. Compds. of the invention inhibited VEGF-stimulated mitogenesis of human vascular endothelial cells in culture with IC₅₀ values between 0.01 μM - 5.0 μM. Thus, I and compns. containing I are useful for the treatment of tyrosine kinase-dependent diseases and conditions, such as angiogenesis, cancer, tumor growth, atherosclerosis, age related macular degeneration, diabetic retinopathy, inflammatory diseases, and the like in mammals (no data).

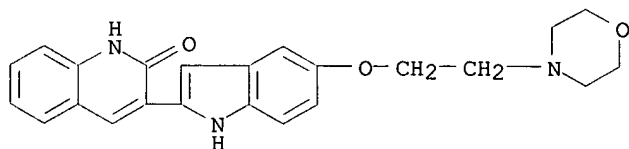
IT **335649-66-6P**, 3-[5-[2-(Morpholin-4-yl)ethoxy]-1H-indol-2-yl]-1H-quinolin-2-one **335649-74-6P**, 3-[5-[3-(Morpholin-4-yl)propoxy]-1H-indol-2-yl]-1H-quinolin-2-one **408502-03-4P**, 3-[5-[3-(4-Methylpiperazin-1-yl)propoxy]-1H-indol-2-yl]-1H-quinolin-2-one

RL: PAC (Pharmacological activity); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)

(tyrosine kinase inhibitor; preparation of (indolyl)quinolinones for treatment of **cancer**, atherosclerosis, inflammatory diseases, and other tyrosine kinase-dependent conditions)

RN 335649-66-6 HCAPLUS

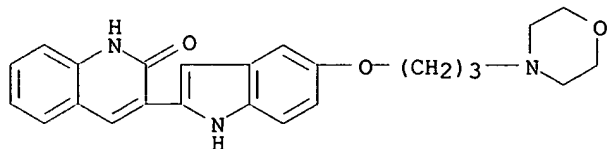
CN 2(1H)-Quinolinone, 3-[5-[2-(4-morpholinyl)ethoxy]-1H-indol-2-yl]- (9CI)
(CA INDEX NAME)



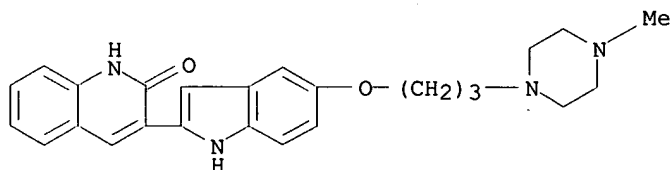
RN 335649-74-6 HCAPLUS

CN 2(1H)-Quinolinone, 3-[5-[3-(4-morpholinyl)propoxy]-1H-indol-2-yl]- (9CI)

(CA INDEX NAME)



RN 408502-03-4 HCAPLUS

CN 2(1H)-Quinolinone, 3-[5-[3-(4-methyl-1-piperazinyl)propoxy]-1H-indol-2-yl]-
(9CI) (CA INDEX NAME)

L72 ANSWER 9 OF 14 HCAPLUS COPYRIGHT 2005 ACS on STN

ACCESSION NUMBER: 2002:868247 HCAPLUS

DOCUMENT NUMBER: 138:148045

TITLE: 15-Deoxy-Δ12,14-prostaglandin J2-induced
apoptosis does not require **PPAR**.AUTHOR(S): **gamma**. in breast cancer cells
Clay, Carl E.; Monjaze, Arta; Thorburn, Jacqueline;
Chilton, Floyd H.; High, Kevin P.CORPORATE SOURCE: Department of Internal Medicine, Section of Pulmonary
Critical Care, Wake Forest University Baptist Medical
Center, Winston Salem, NC, 27157, USASOURCE: Journal of Lipid Research (2002), 43(11), 1818-1828
CODEN: JLPRAW; ISSN: 0022-2275

PUBLISHER: Lipid Research, Inc.

DOCUMENT TYPE: Journal

LANGUAGE: English

AB Naturally occurring derivs. of arachidonic acid are potent agonists for the nuclear hormone **receptor peroxisome proliferator-activated receptor gamma** (**PPARγ**) and block cancer cell proliferation through the induction of apoptosis. The authors have previously reported that induction of apoptosis using cyclopentenone prostaglandins of the J series, including 15-deoxy-Δ12,14-PGJ2 (15dPGJ2), is associated with a high degree of **PPAR**-response element (PPRE) activity and requires early de novo gene expression in breast cancer cells. In the current study, the authors used pharmacol. and genetic approaches to test the hypothesis that **PPARγ** is required for 15dPGJ2-induced apoptosis. The **PPARγ** agonists 15dPGJ2, troglitazone (TGZ), and GW7845, a synthetic and highly selective tyrosine-based **PPARγ** agonist, all increased transcriptional activity of **PPARγ**, and expression of CD36, a **PPARγ**-dependent gene. Transcriptional activity and CD36 expression was reduced by GW9662, a selective and irreversible **PPARγ** antagonist, but GW9662 did not block apoptosis induced by 15dPGJ2. Moreover, dominant neg. expression of **PPARγ** blocked PPRE transcriptional activity, but did not block 15dPGJ2-induced apoptosis. These studies show that while 15dPGJ2 activates PPRE-mediated transcription, **PPARγ** is not required for 15dPGJ2-induced apoptosis in breast cancer cells. Other likely mechanisms

through which cyclopentenone prostaglandins induce apoptosis of cancer cells are discussed.

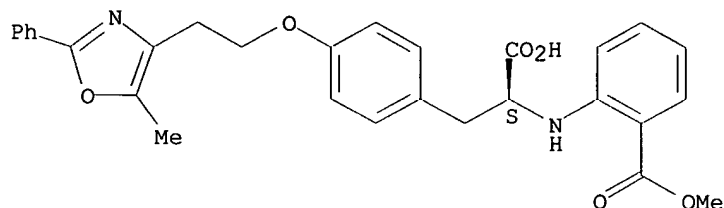
IT 196809-22-0, GW 7845

RL: PAC (Pharmacological activity); BIOL (Biological study)
(PPAR γ agonist; deoxyPGJ2 induction of
apoptosis by mechanism independent of PPAR γ
in breast cancer cells)

RN 196809-22-0 HCAPLUS

CN L-Tyrosine, N-[2-(methoxycarbonyl)phenyl]-O-[2-(5-methyl-2-phenyl-4-oxazolyl)ethyl]- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



REFERENCE COUNT: 79 THERE ARE 79 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L72 ANSWER 10 OF 14 HCAPLUS COPYRIGHT 2005 ACS on STN

ACCESSION NUMBER: 2002:142553 HCAPLUS

DOCUMENT NUMBER: 136:177969

TITLE: Medicinal compositions containing PPAR.

γ . agonists and RXR agonists for
preventing and treating cancer

INVENTOR(S): Kurakata, Shinichi; Fujiwara, Kosaku; Shimazaki,
Naomi; Fujita, Takashi

PATENT ASSIGNEE(S): Sankyo Company, Ltd., Japan

SOURCE: PCT Int. Appl., 40 pp.

CODEN: PIXXD2

DOCUMENT TYPE: Patent

LANGUAGE: Japanese

FAMILY ACC. NUM. COUNT: 1

PATENT INFORMATION:

| PATENT NO. | KIND | DATE | APPLICATION NO. | DATE |
|---|------|----------|-----------------|------------|
| WO 2002013864 | A1 | 20020221 | WO 2001-JP7037 | 20010815 |
| W: AU, BR, CA, CN, CO, CZ, HU, ID, IL, IN, KR, MX, NO, NZ, PL, RU, SG, SK, US, ZA | | | | |
| RW: AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, TR | | | | |
| JP 2002128700 | A2 | 20020509 | JP 2001-241740 | 20010809 |
| AU 2001078738 | A5 | 20020225 | AU 2001-78738 | 20010815 |
| PRIORITY APPLN. INFO.: | | | JP 2000-246910 | A 20000816 |
| | | | WO 2001-JP7037 | W 20010815 |

OTHER SOURCE(S): MARPAT 136:177969

AB Disclosed are medicinal compns. for preventing or treating cancer wherein one or more **Peroxisome proliferator-activated receptor γ (PPAR γ)** activation agonists and one or more retinoid X receptor (RXR) activation agonists are used simultaneously or successively. A combined administration of 5-[4-(6-methoxy-1-methylbenzimidazol-2-ylmethoxy)benzyl]thiazolidine-2,4-dione hydrochloride (I) 5 and targretin 100 mg/kg to HL-60 cell-bearing mice showed synergistic antitumor effect. Also, tablets were prepared from I 0.004, targretin 0.1, lactose 0.244, corn starch 50, and magnesium stearate 0.002 g.

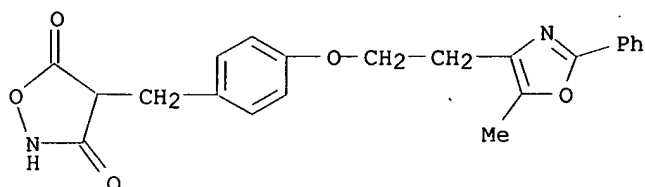
IT 170861-63-9 196808-45-4

RL: THU (Therapeutic use); BIOL (Biological study); USES (Uses)

(simultaneous or successive use of **PPAR γ** agonists and RXR agonists for prevention or treatment of cancer)

RN 170861-63-9 HCAPLUS

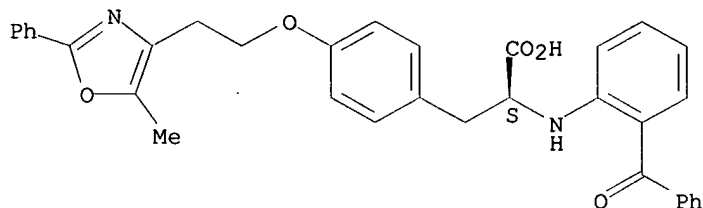
CN 3,5-Isoxazolidinedione, 4-[[4-(2-(5-methyl-2-phenyl-4-oxazolyl)ethoxy)phenyl]methyl]- (9CI) (CA INDEX NAME)



RN 196808-45-4 HCAPLUS

CN L-Tyrosine, N-(2-benzoylphenyl)-O-[2-(5-methyl-2-phenyl-4-oxazolyl)ethyl]- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



REFERENCE COUNT: 17 THERE ARE 17 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L72 ANSWER 11 OF 14 HCAPLUS COPYRIGHT 2005 ACS on STN

ACCESSION NUMBER: 2001:489258 HCAPLUS

DOCUMENT NUMBER: 135:71267

TITLE: Treating cancers associated with overexpression of class I family of receptor tyrosine kinases by use of a strongly binding **PPAR γ** ligand

INVENTOR(S): Dannenberg, Andrew J.; Subbaramaiah, Kotha

PATENT ASSIGNEE(S): Cornell Research Foundation, Inc., USA

SOURCE: PCT Int. Appl., 25 pp.

CODEN: PIXXD2

DOCUMENT TYPE: Patent

LANGUAGE: English

FAMILY ACC. NUM. COUNT: 1

PATENT INFORMATION:

| PATENT NO. | KIND | DATE | APPLICATION NO. | DATE |
|---|------|----------|-----------------|------------|
| WO 2001047555 | A1 | 20010705 | WO 2000-US32442 | 20001211 |
| W: CA | | | | |
| RW: AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, TR | | | | |
| US 6291496 | B1 | 20010918 | US 1999-472179 | 19991227 |
| PRIORITY APPLN. INFO.: | | | US 1999-472179 | A 19991227 |
| AB Cancers associated with overexpression of class I family of receptor tyrosine kinases, e.g., with overexpression of HER-2/neu or overexpression of epidermal growth factor receptor, are treated with strongly binding PPARγ ligands. | | | | |
| IT 196808-45-4 196809-22-0 | | | | |
| RL: BAC (Biological activity or effector, except adverse); BSU (Biological | | | | |

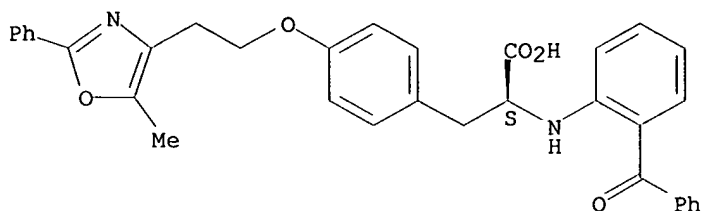
study, unclassified); THU (Therapeutic use); BIOL (Biological study); USES (Uses)

(PPAR γ ligands for treatment of cancers associated with overexpression of class I family of receptor tyrosine kinases)

RN 196808-45-4 HCAPLUS

CN L-Tyrosine, N-(2-benzoylphenyl)-O-[2-(5-methyl-2-phenyl-4-oxazolyl)ethyl]- (9CI) (CA INDEX NAME)

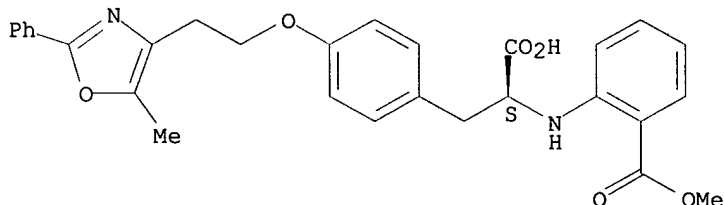
Absolute stereochemistry.



RN 196809-22-0 HCAPLUS

CN L-Tyrosine, N-[2-(methoxycarbonyl)phenyl]-O-[2-(5-methyl-2-phenyl-4-oxazolyl)ethyl]- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



REFERENCE COUNT: 3 THERE ARE 3 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L72 ANSWER 12 OF 14 HCAPLUS COPYRIGHT 2005 ACS on STN

ACCESSION NUMBER: 2000:368081 HCAPLUS

DOCUMENT NUMBER: 133:12750

TITLE: Method using a PPAR γ ligand/agonist for inhibiting angiogenesis and treating tumor growth

INVENTOR(S): Gerritsen, Mary E.; Xin, Xiaohua E.

PATENT ASSIGNEE(S): Genentech, Inc., USA

SOURCE: PCT Int. Appl., 52 pp.

CODEN: PIXXD2

DOCUMENT TYPE: Patent

LANGUAGE: English

FAMILY ACC. NUM. COUNT: 1

PATENT INFORMATION:

| PATENT NO. | KIND | DATE | APPLICATION NO. | DATE |
|---------------|--|----------|-----------------|----------|
| WO 2000030628 | A2 | 20000602 | WO 1999-US27612 | 19991118 |
| WO 2000030628 | A3 | 20011011 | | |
| W: | AE, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CR, CU, CZ, DE, DK, DM, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, UZ, VN, YU, ZA, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM | | | |
| RW: | GH, GM, KE, LS, MW, SD, SL, SZ, TZ, UG, ZW, AT, BE, CH, CY, DE, | | | |

DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF,
 CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG
 CA 2350599 AA 20000602 CA 1999-2350599 19991118
 EP 1143953 A2 20011017 EP 1999-960538 19991118
 EP 1143953 A3 20020206
 R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT,
 IE, SI, LT, LV, FI, RO
 US 2001036955 A1 20011101 US 2001-865859 20010525
 PRIORITY APPLN. INFO.: US 1998-109328P P 19981120
 US 1999-116530P P 19990120
 US 1999-443010 B1 19991117
 WO 1999-US27612 W 19991118

OTHER SOURCE(S): MARPAT 133:12750

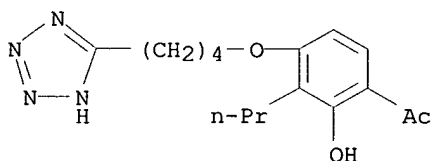
AB Angiogenesis is inhibited and the growth of tumors is treated by
 administering an effective amount of a **PPAR γ**
 ligand/agonist, optionally with an RXR receptor ligand.

IT **88107-10-2**, LY 171883

RL: BAC (Biological activity or effector, except adverse); BSU (Biological
 study, unclassified); BIOL (Biological study)
 (**PPAR γ** ligand/agonist for inhibiting
 angiogenesis and treating **tumor** growth)

RN 88107-10-2 HCAPLUS

CN Ethanone, 1-[2-hydroxy-3-propyl-4-[4-(1H-tetrazol-5-yl)butoxy]phenyl]-
 (9CI) (CA INDEX NAME)



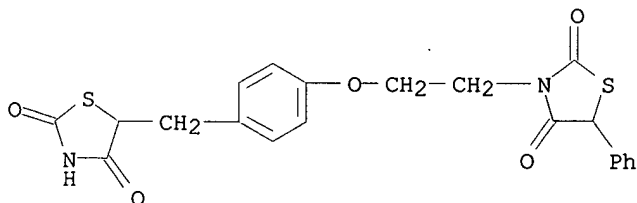
IT **143811-62-5**

RL: BAC (Biological activity or effector, except adverse); BSU (Biological
 study, unclassified); THU (Therapeutic use); BIOL (Biological study); USES
 (Uses)

(**PPAR γ** ligand/agonist for inhibiting
 angiogenesis and treating **tumor** growth)

RN 143811-62-5 HCAPLUS

CN 2,4-Thiazolidinedione, 3-[2-[4-[(2,4-dioxo-5-thiazolidinyl)methyl]phenoxy]
 ethyl]-5-phenyl- (9CI) (CA INDEX NAME)



L72 ANSWER 13 OF 14 HCAPLUS COPYRIGHT 2005 ACS on STN

ACCESSION NUMBER: 2000:52487 HCAPLUS

DOCUMENT NUMBER: 132:202817

TITLE: Activation of **peroxisome**
proliferator-activated

receptor γ does not inhibit

IL-6 or TNF- α responses of macrophages to
 lipopolysaccharide in vitro or in vivo

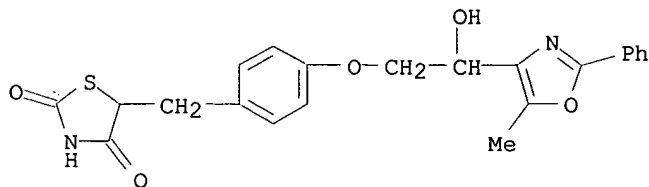
AUTHOR(S): Thieringer, Rolf; Fenyk-Melody, Judy E.; Le Grand,
 Cheryl B.; Shelton, Beverly A.; Detmers, Patricia A.;

CORPORATE SOURCE: Somers, Elizabeth P.; Carbin, Linda; Moller, David E.; Wright, Samuel D.; Berger, Joel
 SOURCE: Departments of Endocrinology and Chemical Biology, Merck Research Laboratories, Rahway, NJ, 07065, USA
 PUBLISHER: Journal of Immunology (2000), 164(2), 1046-1054
 DOCUMENT TYPE: CODEN: JOIMA3; ISSN: 0022-1767
 LANGUAGE: American Association of Immunologists
 Journal
 English

AB The authors investigated the potential use of **peroxisome proliferator-activated receptor .gamma** (**PPAR γ**) agonists as anti-inflammatory agents in cell-based assays and in a mouse model of endotoxemia. Human peripheral blood monocytes were treated with LPS or PMA and a variety of **PPAR γ** agonists. Although 15-deoxy- $\Delta^{12,14}$ -prostaglandin J2 (15d-PGJ2) at micromolar concns. inhibited the production of TNF- α and IL-6, 4 other high affinity **PPAR.gamma** ligands failed to affect cytokine production. Similar results were obtained when the monocytes were allowed to differentiate in culture into macrophages that expressed higher levels of **PPAR.gamma** or when the murine macrophage cell line RAW 264.7 was used. Furthermore, saturating concns. of a potent **PPAR γ** ligand not only failed to block cytokine production, but also were unable to block the inhibitory activity of 15d-PGJ2. Thus, activation of **PPAR γ** does not appear to inhibit the production of cytokines by either monocytes or macrophages, and the inhibitory effect observed with 15d-PGJ2 is most likely mediated by a **PPAR.gamma**-independent mechanism. To examine the anti-inflammatory activity of **PPAR γ** agonists in vivo, db/db mice were treated with a potent thiazolidinedione that lowered their elevated blood glucose and triglyceride levels as expected. When thiazolidinedione-treated mice were challenged with LPS, they displayed no suppression of cytokine production. Rather, their blood levels of TNF- α and IL-6 were elevated beyond the levels observed in control db/db mice challenged with LPS. Comparable results were obtained with the corresponding lean mice. Thus, compds. capable of activating **PPAR γ** in leukocytes will not be useful for the treatment of acute inflammation.

IT 103788-05-2, AD5075
 RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
 (peroxisome proliferator-activated , receptor γ activation by agonists does not inhibit interleukin-6 or tumor necrosis factor α responses of macrophages to lipopolysaccharide)

RN 103788-05-2 HCAPLUS
 CN 2,4-Thiazolidinedione, 5-[[4-[2-hydroxy-2-(5-methyl-2-phenyl-4-oxazolyl)ethoxy]phenyl]methyl]- (9CI) (CA INDEX NAME)



REFERENCE COUNT: 44 THERE ARE 44 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L72 ANSWER 14 OF 14 HCAPLUS COPYRIGHT 2005 ACS on STN
 ACCESSION NUMBER: 1999:778252 HCAPLUS
 DOCUMENT NUMBER: 132:87867

TITLE: A new ligand for the **peroxisome proliferator-activated receptor- γ** (PPAR-**gamma**.), GW7845, inhibits rat mammary carcinogenesis

AUTHOR(S): Suh, Nanjoo; Wang, Yongping; Williams, Charlotte R.; Risingsong, Renee; Gilmer, Tona; Willson, Timothy M.; Sporn, Michael B.

CORPORATE SOURCE: Department of Pharmacology and Norris Cotton Cancer Center, Dartmouth Medical School, Hanover, NH, 03755, USA

SOURCE: Cancer Research (1999), 59(22), 5671-5673
CODEN: CNREA8; ISSN: 0008-5472

PUBLISHER: AACR Subscription Office

DOCUMENT TYPE: Journal

LANGUAGE: English

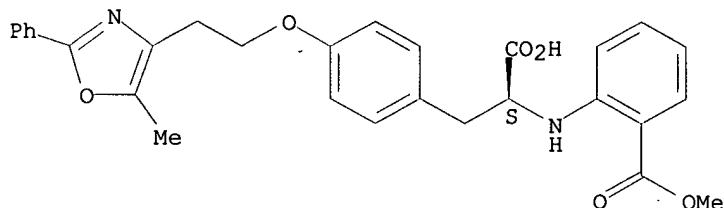
AB We have tested a new ligand for **PPAR- γ** receptor, GW7845, as an inhibitor of exptl. mammary carcinogenesis, using the classic rat model with nitrosomethylurea as carcinogen. Rats were first treated with a single dose of nitrosomethylurea (50 mg/kg body weight, i.p.). Starting 1 wk later, they were fed GW7845, at either 60 or 30 mg/kg of diet, for 2 mo. This agent significantly reduced tumor incidence, tumor number, and tumor weight at both doses. This is the first report of the use of a ligand for **peroxisome proliferator-activated receptor- γ** to prevent exptl. breast cancer.

IT 196809-22-0, GW 7845
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(ligand for **PPAR- γ** receptor, GW7845, for prevention of breast **cancer**)

RN 196809-22-0 HCAPLUS

CN L-Tyrosine, N-[2-(methoxycarbonyl)phenyl]-O-[2-(5-methyl-2-phenyl-4-oxazolyl)ethyl]- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



REFERENCE COUNT: 28 THERE ARE 28 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

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| L1 | STR |
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| L46 | STR |
| L51 | STR |
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 L57 839 SEA FILE=REGISTRY SSS FUL L5 AND (L8 OR L9 OR L10)
 L59 2611 SEA FILE=REGISTRY SSS FUL L30 AND (L8 OR L9 OR L10)
 L60 2264 SEA FILE=REGISTRY SSS FUL L37 AND (L8 OR L9 OR L10)
 L61 364 SEA FILE=REGISTRY SSS FUL L42 AND (L8 OR L9 OR L10)
 L62 37956 SEA FILE=REGISTRY SSS FUL L46 AND (L8 OR L9 OR L10)
 L63 969 SEA FILE=REGISTRY SSS FUL L51 AND (L8 OR L9 OR L10)
 L64 92378 SEA FILE=REGISTRY ABB=ON PLU=ON L55 OR L56 OR L57 OR L59 OR
 L60 OR L61 OR L62 OR L63
 L65 14878 SEA FILE=HCAPLUS ABB=ON PLU=ON L64
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 .1/BI OR PPAR2/BI OR PPAR4/BI OR PPAR1/BI
 OR PPARFS/BI)
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 PT?(L) GAMMA
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 L69 5023 SEA FILE=HCAPLUS ABB=ON PLU=ON (PEROXISOME(W) PROLIFER?(W) ACTI
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 L81 698 SEA FILE=HCAPLUS ABB=ON PLU=ON L65 AND (BENZOIC? OR NICOTINI?
) (2A) ACID
 L82 67 SEA FILE=HCAPLUS ABB=ON PLU=ON L81 AND L71
 L83 17 SEA FILE=HCAPLUS ABB=ON PLU=ON L82 AND PENTA?
 L84 31 SEA FILE=HCAPLUS ABB=ON PLU=ON L83 OR L72
 L85 1 SEA FILE=HCAPLUS ABB=ON PLU=ON L84 AND PD=<DECEMBER 31, 1996
 L86 1 SEA FILE=HCAPLUS ABB=ON PLU=ON L84 NOT (2005 OR 2004 OR 2003
 OR 2002 OR 2001 OR 2000 OR 1999 OR 1998 OR 1997)/PY
 L87 1 SEA FILE=HCAPLUS ABB=ON PLU=ON L85 OR L86

=> d ibib abs hitstr l87 1

L87 ANSWER 1 OF 1 HCAPLUS COPYRIGHT 2005 ACS on STN

ACCESSION NUMBER: 1964:12243 HCAPLUS

DOCUMENT NUMBER: 60:12243

ORIGINAL REFERENCE NO.: 60:2198b-e

TITLE: Relation between chemical structure and antitumor
action of alkylating compounds

AUTHOR(S): Berlin, A. Ya.

SOURCE: Tr. Inst. Eksperim. i Klinich. Onkol., Akad. Med. Nauk
SSSR (1960), 2, 15-28

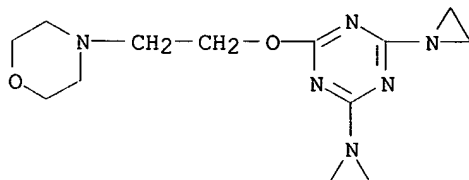
DOCUMENT TYPE: Journal

LANGUAGE: Unavailable

AB A discussion is presented of the relation between the hydrolysis rate and antitumor action of compds. of the type 4-RC6H4N-(CH₂CH₂Cl)₂, where R is COOH, CH₂COOH, CH₂CH₂COOH, CH₂CH₂CH₂COOH, CH₂CH₂CH₂CH₂COOH, OCH₂COOH, OCH₂CH₂COOH, OCH₂CH₂CH₂COOH, or OCH₂CH₂CH₂CH₂-COOH and compds. of the type MeSO₂O(CH₂)_nOSO₂Me, where n is 2, 3, 4, 5, 6, 7, 8, 9, or 10, and aromatic chloroethyl amines 2-MeOC₆H₄N(CH₂CH₂Cl)₂, 4-MeOC₆H₄N(CH₂CH₂Cl)₂, PhN(CH₂CH₂Cl)₂, and PhN(Et)CH₂CH₂Cl. For characterizing antitumor action the value "molar activity" is proposed, expressed by the formula Am = 100T.M/D, where T is the % inhibition of tumors, M is the mol. weight of the preparation, and D is the dose in mg./kg. at a daily injection for 15-21 days. Values are given for Am for Sarcoma 45 and Ehrlich's tumor for: sarcolysine (I), I derivs. of the type 4-(ClCH₂)₂NC₆H₄CH₂C(NHR)-COOH, where R is CHO or Ac, and I derivs. of the type 4-(Cl-CH₂CH₂)₂NC₆H₄CH₂CH(NH₂)COOR.HCl, where R is Et, iso-Pr, or Bu; 2,5-disubstituted 6-ethyleniminobenzoquinones, where the 2- and 5-substituents are, resp.: H and H; Cl and H; Cl and Cl; EtO and EtO; PrO and PrO; derivs. of pyrimidine, where 2,6,5,4-substituents are, resp.: OH, Me, (ClCH₂CH₂)₂N, OH; Cl, Me, (ClCH₂CH₂)₂N, Cl; ethylenimino, Me, NO₂, ethylenimino; OH, Me, [CH₂CH₂N]P(:O)CH₂, OH; ethylenimino, Cl, H,

ethylenimino; derivs. of 2,6-bis(ethylenimino)triazines where the 4-substituent is: ethylenimino, NH₂, MeNH, PhCH₂NH, piperidino, morpholino, β-piperidinoethylamino, β-morpholinoethylamino, MeO, PhCH₂O, Et₂NCH₂CH₂O, β-piperidinoethoxy, or β-morpholinoethoxy. From Reference Zh., Biol. Khim. 1963, Abstract Number 14F1308.

IT 72239-63-5, s-Triazine, 2,4-bis(1-aziridinyl)-6-(2-morpholinoethoxy)-
(neoplasm inhibition by)
RN 72239-63-5 HCAPLUS
CN 1,3,5-Triazine, 2,4-bis(1-aziridinyl)-6-[2-(4-morpholinyl)ethoxy]- (9CI)
(CA INDEX NAME)



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| L42 | STR |
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| L69 | 5023 SEA FILE=HCAPLUS ABB=ON PLU=ON (PEROXISOME(W) PROLIFER?(W) ACTIVAT?(5A) RECEPT? OR PPAR) (L) GAMMA |
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| L72 | 14 SEA FILE=HCAPLUS ABB=ON PLU=ON L71 AND L70 |
| L81 | 698 SEA FILE=HCAPLUS ABB=ON PLU=ON L65 AND (BENZOIC? OR NICOTINI?) (2A) ACID |
| L82 | 67 SEA FILE=HCAPLUS ABB=ON PLU=ON L81 AND L71 |
| L83 | 17 SEA FILE=HCAPLUS ABB=ON PLU=ON L82 AND PENTA? |
| L84 | 31 SEA FILE=HCAPLUS ABB=ON PLU=ON L83 OR L72 |

L85 1 SEA FILE=HCAPLUS ABB=ON PLU=ON L84 AND PD=<DECEMBER 31, 1996
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 OR 2002 OR 2001 OR 2000 OR 1999 OR 1998 OR 1997)/PY
 L87 1 SEA FILE=HCAPLUS ABB=ON PLU=ON L85 OR L86
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 OR 2002 OR 2001 OR 2000 OR 1999 OR 1998 OR 1997)/PY
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 ?PHARMA? OR ?DRUG?)
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=> d ibib abs hitstr 191 1-11

L91 ANSWER 1 OF 11 HCAPLUS COPYRIGHT 2005 ACS on STN

ACCESSION NUMBER: 1996:656494 HCAPLUS

DOCUMENT NUMBER: 126:372

TITLE: Structure-activity relationship studies on benzofuran
 analogs of propafenone-type modulators of tumor cell
 multidrug resistance

AUTHOR(S): Ecker, Gerhard; Chiba, Peter; Hitzler, Manuela;
 Schmid, Diethard; Visser, Klaus; Cordes, Hans Peter;
 Csoellei, Josef; Seydel, Joachim K.; Schaper,
 Klaus-Juergen

CORPORATE SOURCE: Institute of Pharmaceutical Chemistry, University of
 Vienna, Vienna, A-1090, Austria

SOURCE: Journal of Medicinal Chemistry (1996), 39(24),
 4767-4774

CODEN: JMCMAR; ISSN: 0022-2623

PUBLISHER: American Chemical Society

DOCUMENT TYPE: Journal

LANGUAGE: English

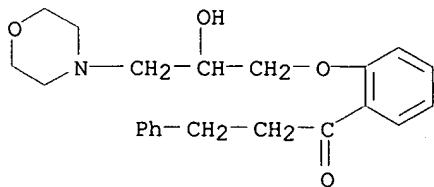
AB A series of benzofurylethanolamine analogs of propafenone have been prepared
 and evaluated for multidrug resistance-reversing activity in two in vitro
 assay systems. As for propafenones, an excellent correlation of biol.
 data with calculated lipophilicity values was found for benzofurans, whereby
 the latter generally had lower activity/lipophilicity ratios. Almost
 identical slopes of the regression lines were obtained for both
 propafenones and benzofurans. Multiple linear regression anal. of the
 complete data set yielded an equation with excellent predictive power
 ($r^2_{\text{cross-valid}} = 0.968$). Interaction measurements with artificial
 membranes indicated that the differences in activity between these two
 series of compds. are not due to differences in the interaction pattern
 with biol. membranes.

IT 86383-89-3 183014-30-4 183014-34-8

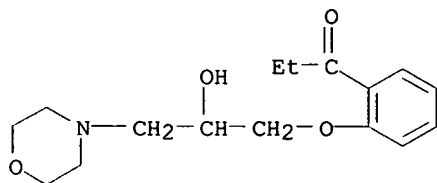
RL: BAC (Biological activity or effector, except adverse); BPR (Biological
 process); BSU (Biological study, unclassified); PRP (Properties); THU
 (Therapeutic use); BIOL (Biological study); PROC (Process); USES (Uses)
 (structure-activity relationship studies on benzofuran analogs of
 propafenone as modulators of **tumor cell multidrug**
 resistance in relation to lipophilicity and interaction with artificial
 membranes)

RN 86383-89-3 HCAPLUS

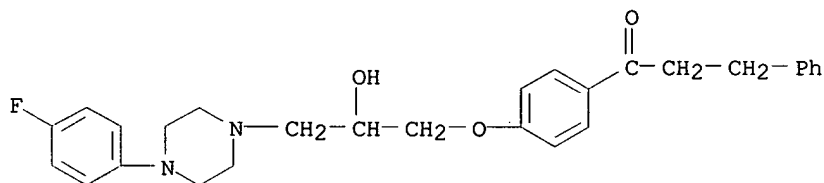
CN 1-Propanone, 1-[2-[2-hydroxy-3-(4-morpholinyl)propoxy]phenyl]-3-phenyl-
 (9CI) (CA INDEX NAME)



RN 183014-30-4 HCAPLUS
 CN 1-Propanone, 1-[2-[2-hydroxy-3-(4-morpholinyl)propoxy]phenyl]- (9CI) (CA INDEX NAME)



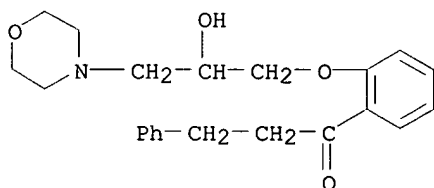
RN 183014-34-8 HCAPLUS
 CN 1-Propanone, 1-[4-[3-[4-(4-fluorophenyl)-1-piperazinyl]-2-hydroxypropoxy]phenyl]-3-phenyl- (9CI) (CA INDEX NAME)



IT 86383-06-4P
 RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); PRP (Properties); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)

(structure-activity relationship studies on benzofuran analogs of propafenone as modulators of tumor cell multidrug resistance in relation to lipophilicity and interaction with artificial membranes)

RN 86383-06-4 HCAPLUS
 CN 1-Propanone, 1-[2-[2-hydroxy-3-(4-morpholinyl)propoxy]phenyl]-3-phenyl-, hydrochloride (9CI) (CA INDEX NAME)



● HCl

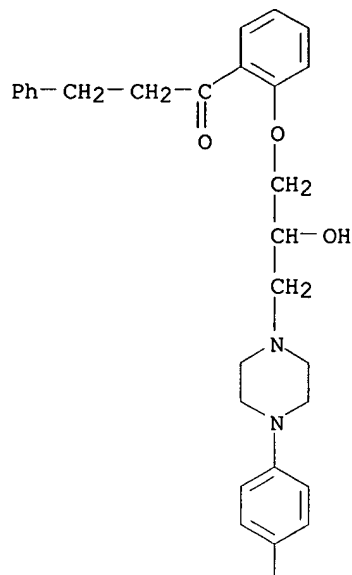
IT 163858-57-9 163858-59-1 178691-48-0
 RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); PRP (Properties); THU (Therapeutic use); BIOL (Biological study); USES (Uses)

(structure-activity relationship studies on benzofuran analogs of propafenone as modulators of tumor cell multidrug resistance in relation to lipophilicity and interaction with artificial membranes)

RN 163858-57-9 HCAPLUS

CN 1-Propanone, 1-[2-[2-hydroxy-3-[4-(4-methoxyphenyl)-1-piperazinyl]propoxy]phenyl]-3-phenyl- (9CI) (CA INDEX NAME)

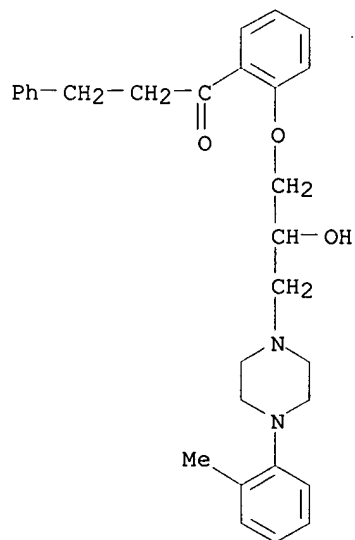
PAGE 1-A



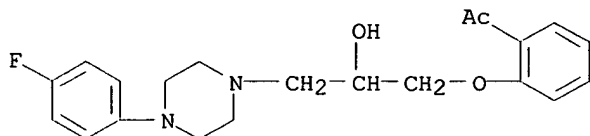
PAGE 2-A

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RN 163858-59-1 HCAPLUS
CN 1-Propanone, 1-[2-[2-hydroxy-3-[4-(2-methylphenyl)-1-piperazinyl]propoxy]phenyl]-3-phenyl- (9CI) (CA INDEX NAME)



RN 178691-48-0 HCAPLUS
 CN Ethanone, 1-[2-[3-[4-(4-fluorophenyl)-1-piperazinyl]-2-hydroxypropoxy]phenyl]- (9CI) (CA INDEX NAME)



L91 ANSWER 2 OF 11 HCAPLUS COPYRIGHT 2005 ACS on STN

ACCESSION NUMBER: 1996:200808 HCAPLUS

DOCUMENT NUMBER: 124:278313

TITLE: Transport properties of the multidrug resistance-associated protein (MRP) in human tumor cells

AUTHOR(S): Hollo, Zsolt; Homolya, Laszlo; Heged+dblac;us, Tamas; Sarkadi, Balazs

CORPORATE SOURCE: National Institute of Haematology and Immunology, Daroczi u. 24, Budapest, H-1113, Hung.

SOURCE: FEBS Letters (1996), 383(1,2), 99-104

CODEN: FEBLAL; ISSN: 0014-5793

PUBLISHER: Elsevier

DOCUMENT TYPE: Journal

LANGUAGE: English

AB In this paper we demonstrate that the expression of the multidrug resistance-associated protein (MRP) in a variety of intact human tumor cells results in the ATP-dependent, mutually exclusive extrusion of both the acetoxymethyl ester and the free anion forms of the fluorescent dye calcein, as well as that of a fluorescent pyrenemaleimide-glutathione conjugate. The MRP-dependent transport of all these three model compds. closely correlates with the expression level of MRP and is cross-inhibited by hydrophobic anticancer drugs, by reversing agents for MDR1, and also by compds. not influencing MDR1, such as hydrophobic anions, alkylating agents, and inhibitors of organic anion transporters. Cellular glutathione depletion affects neither the MRP-dependent extrusion of calcein AM or free calcein, nor its modulation by most hydrophobic or anionic compds., although eliminating the cross-inhibitory effect of glutathione conjugates. These results suggest that the outward pumping of both hydrophobic uncharged and water-soluble anionic compds., including glutathione conjugates, is an inherent property of MRP, and offer sensitive methods for the functional diagnostics of this transport protein as well as for the rapid screening of drug-resistance modulating agents.

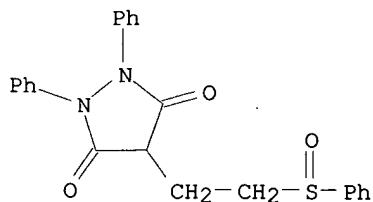
IT 57-96-5, Sulfinpyrazone

RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); BIOL (Biological study)

(transport properties of **multidrug** resistance-associated protein in human **tumor** cells)

RN 57-96-5 HCAPLUS

CN 3,5-Pyrazolidinedione, 1,2-diphenyl-4-[2-(phenylsulfinyl)ethyl]- (6CI, 7CI, 8CI, 9CI) (CA INDEX NAME)



L91 ANSWER 3 OF 11 HCAPLUS COPYRIGHT 2005 ACS on STN

ACCESSION NUMBER: 1995:872796 HCAPLUS

DOCUMENT NUMBER: 123:329465

TITLE: Relationship between multidrug resistant gene expression and multidrug resistant-reversing effect of MS-209 in various tumor cells

AUTHOR(S): Baba, Makoto; Nakanishi, Osamu; Sato, Wakao; Saito, Akiko; Miyama, Yukio; Yano, Osamu; Shimada, Shizuo; Fukazawa, Nobuyuki; Naito, Mikihiro; Tsuruo, Takashi
CORPORATE SOURCE: Institute Biological Science, Mitsui Pharmaceuticals, Inc., Mobara, 297, Japan

SOURCE: Cancer Chemotherapy and Pharmacology (1995), 36(5), 361-7

CODEN: CCPHDZ; ISSN: 0344-5704

PUBLISHER: Springer

DOCUMENT TYPE: Journal

LANGUAGE: English

AB MS-209 is a novel quinoline compound which can overcome multidrug resistance (MDR) both in vitro and in vivo, while having a low level of side effects, and is now being evaluated in a clin. phase II study. Reverse transcription-polymerase chain reaction (RT-PCR) was used to quantitate the expression levels of MDR genes in various mouse and human tumor cell lines. The MDR gene and the β actin gene, as the internal reference standard, were coamplified sep., and the relative expression of the MDR gene was represented by the MDR/ β actin ratio. The in vitro MDR-reversing effect of MS-209 was then compared with the MDR gene expression (MDR/ β actin ratio). The authors found a significant correlation between these two parameters. Moreover, a significant correlation was also observed between the level of expression of the MDR1 gene and that of P-glycoprotein in human cell lines. Therefore, the efficacy of MS-209 seems to specifically depend on the level of MDR gene expression (P-glycoprotein). From these observations, it is suggested that RT-PCR assays of MDR1 gene in tumor biopsy specimens might be an effective means to predict the response of tumor cells to combination therapy with MS-209.

IT 158681-49-3, MS-209

RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); THU (Therapeutic use); BIOL (Biological study); USES (Uses)

(relationship between **multidrug** resistant gene expression and **multidrug** resistant-reversing effect of MS-209 in various **tumor** cells in relation to combination **therapy** in human and laboratory animal cells)

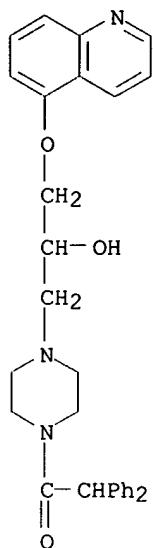
RN 158681-49-3 HCAPLUS

CN 1-Piperazineethanol, 4-(diphenylacetyl)- α -[(5-quinolinyloxy)methyl]-, (2E)-2-butenedioate (2:3) (salt) (9CI) (CA INDEX NAME)

CM 1

CRN 129716-58-1

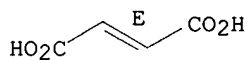
CMF C30 H31 N3 O3



CM 2

CRN 110-17-8
CMF C4 H4 O4

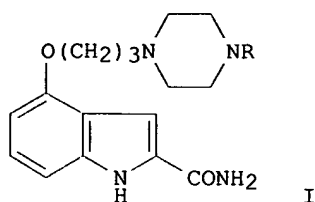
Double bond geometry as shown.



L91 ANSWER 4 OF 11 HCAPLUS COPYRIGHT 2005 ACS on STN
 ACCESSION NUMBER: 1995:761990 HCAPLUS
 DOCUMENT NUMBER: 123:286095
 TITLE: Amines to sensitize multidrug-resistant cells
 INVENTOR(S): Abraham, Irene; Hester, Jackson B., Jr.
 PATENT ASSIGNEE(S): Upjohn Co., USA
 SOURCE: U.S., 20 pp. Cont.-in-part of U.S. Ser. No. 682,809,
 abandoned.
 CODEN: USXXAM
 DOCUMENT TYPE: Patent
 LANGUAGE: English
 FAMILY ACC. NUM. COUNT: 2
 PATENT INFORMATION:

| PATENT NO. | KIND | DATE | APPLICATION NO. | DATE |
|------------------------|------|----------|-----------------|-------------|
| US 5436337 | A | 19950725 | US 1993-132515 | 19931006 |
| PRIORITY APPLN. INFO.: | | | US 1993-132515 | B2 19931006 |
| | | | US 1991-682809 | 19910409 |

GI



AB The piperazines I [R = CHPh₂, 2,4-dipyrrolidino-6-pyrimidinyl] were prepared for use as sensitizers for anticancer therapy. Thus, 4-benzyloxyindole-2-carboxylic acid was amidated, debenzylated, and alkylated to give I [R = CHPh₂], which was dehydrated to the nitrile (II). II was combined with adriamycin to treat drug-resistant pancreatic carcinoma. Steroidal amines, alkylamines, bicyclic amines, bicyclic ethers, and naphthoxazines are also useful in treating individuals who have cancer that has become resistant to cancer chemotherapeutic agents and in preventing the resistance from developing or slowing the rate of resistance to the chemotherapeutic agents.

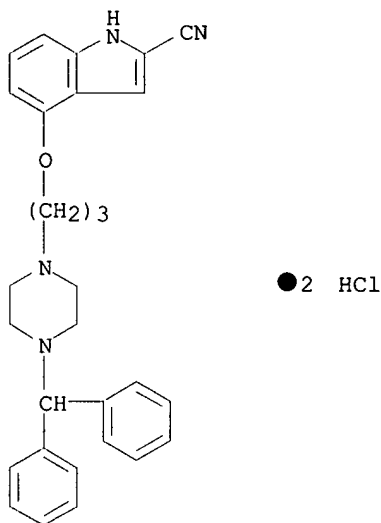
IT 145521-35-3P

RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)

(piperazinopropoxyindolecarboxamides in preparation of **anticancer drug** sensitizers)

RN 145521-35-3 HCAPLUS

CN 1H-Indole-2-carbonitrile, 4-[3-[4-(diphenylmethyl)-1-piperazinyl]propoxy]-, dihydrochloride (9CI) (CA INDEX NAME)



IT 145033-49-4

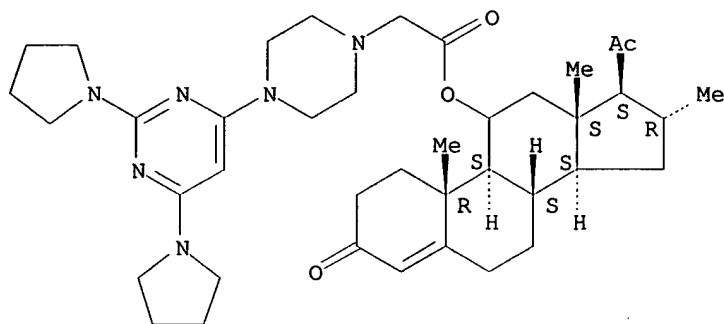
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); THU (Therapeutic use); BIOL (Biological study); USES (Uses)

(piperazinopropoxyindolecarboxamides in preparation of **anticancer drug** sensitizers)

RN 145033-49-4 HCAPLUS

CN Pregn-4-ene-3,20-dione, 11-[[[4-(2,6-di-1-pyrrolidinyl-4-pyrimidinyl)-1-piperazinyl]acetyl]oxy]-16-methyl-, (16α)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



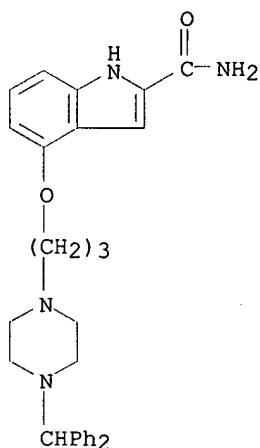
IT 145014-50-2P

RL: RCT (Reactant); SPN (Synthetic preparation); THU (Therapeutic use);
BIOL (Biological study); PREP (Preparation); RACT (Reactant or reagent);
USES (Uses)

(piperazinopropoxyindolecarboxamides in preparation of **anticancer**
drug sensitizers)

RN 145014-50-2 HCAPLUS

CN 1H-Indole-2-carboxamide, 4-[3-[4-(diphenylmethyl)-1-piperazinyl]propoxy]-
(9CI) (CA INDEX NAME)



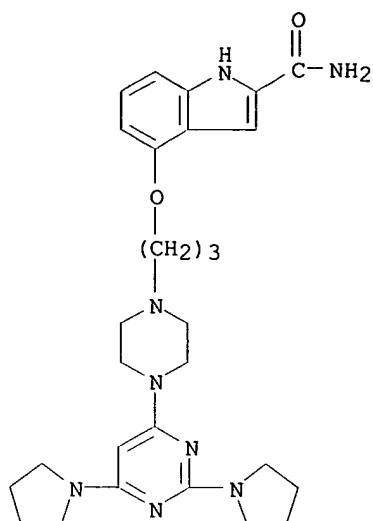
IT 145014-51-3P 145014-53-5P

RL: SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological
study); PREP (Preparation); USES (Uses)

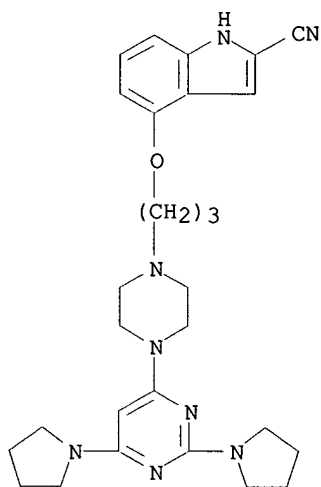
(piperazinopropoxyindolecarboxamides in preparation of **anticancer**
drug sensitizers)

RN 145014-51-3 HCAPLUS

CN 1H-Indole-2-carboxamide, 4-[3-[4-(2,6-di-1-pyrrolidinyl-4-pyrimidinyl)-1-
piperazinyl]propoxy]- (9CI) (CA INDEX NAME)



RN 145014-53-5 HCAPLUS
 CN 1H-Indole-2-carbonitrile, 4-[3-[4-(2,6-di-1-pyrrolidinyl-4-pyrimidinyl)-1-piperazinyl]propoxy]- (9CI) (CA INDEX NAME)



L91 ANSWER 5 OF 11 HCAPLUS COPYRIGHT 2005 ACS on STN
 ACCESSION NUMBER: 1995:87624 HCAPLUS
 DOCUMENT NUMBER: 122:426
 TITLE: The arotinoid Ro 40-8757 has antiproliferative effects in drug-resistant human colon and breast cancer cell lines in vitro
 AUTHOR(S): Louvet, Christophe; Empereur, Sylvie; Fagot, Dominique; Forgue-Lafitte, Elisabeth; Chastre, Eric; Zimmer, Amazia; Mester, Jan; Gespach, Christian
 CORPORATE SOURCE: INSERM U55, Paris, 75012, Fr.
 SOURCE: Cancer Letters (Shannon, Ireland) (1994), 85(1), 83-6
 CODEN: CALEDQ; ISSN: 0304-3835
 DOCUMENT TYPE: Journal
 LANGUAGE: English
 AB We have examined the antiproliferative effects of the arotinoid Ro 40-8757

in 3 drug-resistant human adenocarcinoma cell lines: the colonic cells HT29-5FU and CaCo2, and the mammary cells MCF-7mdr1. Whereas all-trans retinoic acid had no effect at the concentration of 10^{-6} M, Ro 40-8757 was found to exert a high antiproliferative action with similar inhibitory potency (IC_{50}) in drug-resistant and parental cell lines (range, $0.06 + 10^{-6}$ to $0.57 + 10^{-6}$ M). We conclude that: (1) thymidylate synthase is not involved in the mechanism of action of Ro 40-8757; (2) the mdr1 gene product does not recognize this retinoic derivative; and (3) Ro 40-8757, alone or in combinations with other cytotoxic drugs, can be very useful in patients with progressive disease after conventional chemotherapy.

IT 125533-88-2, Ro 40-8757

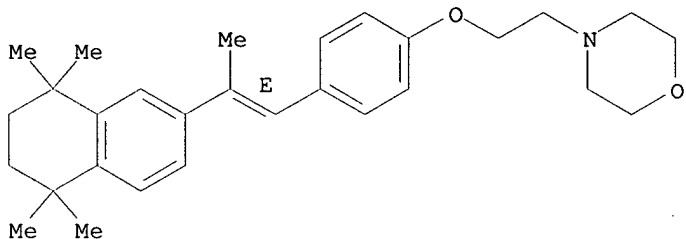
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); THU (Therapeutic use); BIOL (Biological study); USES (Uses)

(arotinoid Ro 40-8757 has antiproliferative effects in drug-resistant human colon and breast cancer cell lines in vitro)

RN 125533-88-2 HCAPLUS

CN Morpholine, 4-[2-[4-[(1E)-2-(5,6,7,8-tetrahydro-5,5,8,8-tetramethyl-2-naphthalenyl)-1-propenyl]phenoxy]ethyl]- (9CI) (CA INDEX NAME)

Double bond geometry as shown.



L91 ANSWER 6 OF 11 HCAPLUS COPYRIGHT 2005 ACS on STN

ACCESSION NUMBER: 1993:52416 HCAPLUS

DOCUMENT NUMBER: 118:52416

TITLE: Use of amines to sensitize multidrug-resistant cells

INVENTOR(S): Abraham, Irene; Hester, Jackson Boling

PATENT ASSIGNEE(S): Upjohn Co., USA

SOURCE: PCT Int. Appl., 77 pp.

CODEN: PIXXD2

DOCUMENT TYPE: Patent

LANGUAGE: English

FAMILY ACC. NUM. COUNT: 2

PATENT INFORMATION:

| PATENT NO. | KIND | DATE | APPLICATION NO. | DATE |
|--|------|----------|-----------------|-------------|
| WO 9218089 | A2 | 19921029 | WO 1992-US2237 | 19920327 |
| WO 9218089 | A3 | 19930304 | | |
| W: AU, BB, BG, BR, CA, CS, FI, HU, JP, KP, KR, LK, MG, MN, MW, NO, PL, RO, RU, SD, US | | | | |
| RW: AT, BE, BF, BJ, CF, CG, CH, CI, CM, DE, DK, ES, FR, GA, GB, GN, GR, IT, LU, MC, ML, MR, NL, SE, SN, TD, TG | | | | |
| AU 9217738 | A1 | 19921117 | AU 1992-17738 | 19920327 |
| EP 579754 | A1 | 19940126 | EP 1992-910802 | 19920327 |
| R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, MC, NL, SE | | | | |
| PRIORITY APPLN. INFO.: | | | US 1991-682809 | A2 19910409 |
| | | | WO 1992-US2237 | A 19920327 |

OTHER SOURCE(S): MARPAT 118:52416

AB Multidrug resistance to cancer therapeutic agents in human cancer patients is treated by administering a sensitizing agent comprising a steroidal, aliphatic, or bicyclic amine, a bicyclic or tricyclic ether, or an indole derivative (Markush structures given). Thus, in a patient with pancreatic carcinoma treated with Adriamycin, the development of Adriamycin

resistance was reversed by treatment with 4-[3-[4-(diphenylmethyl)-1-piperazinyl]propoxy]indole-2-carboxamide (I) (0.01-5.0 mg/kg/h over 5 days). I was prepared by amidation of 4-(benzyloxy)indole-2-carboxylic acid, catalytic hydrogenation, and condensation of the product 4-hydroxyindole-2-carboxamide with 1-chloro-3-[4-(diphenylmethyl)-1-piperazinyl]propane.

IT 122004-37-9 145014-50-2 145014-51-3

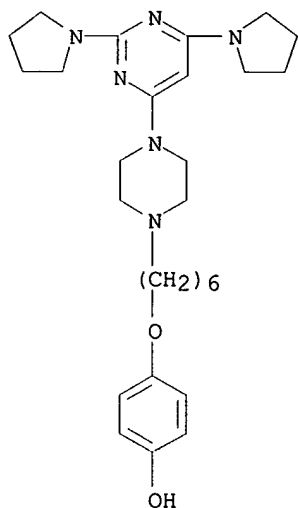
145014-52-4 145014-53-5 145033-49-4

RL: BIOL (Biological study)

(multidrug resistance to neoplasm inhibitors reversal by)

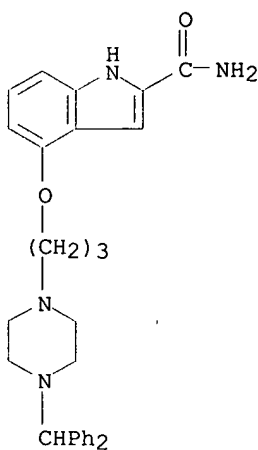
RN 122004-37-9 HCAPLUS

CN Phenol, 4-[[6-[4-(2,6-di-1-pyrrolidinyl-4-pyrimidinyl)-1-piperazinyl]hexyl]oxy]- (9CI) (CA INDEX NAME)



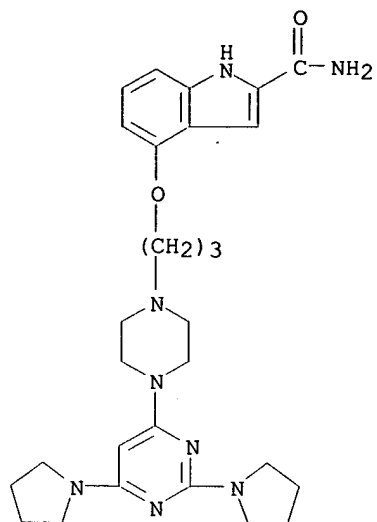
RN 145014-50-2 HCAPLUS

CN 1H-Indole-2-carboxamide, 4-[3-[4-(diphenylmethyl)-1-piperazinyl]propoxy]- (9CI) (CA INDEX NAME)

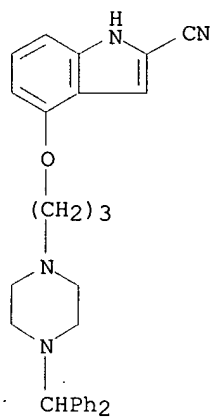


RN 145014-51-3 HCAPLUS

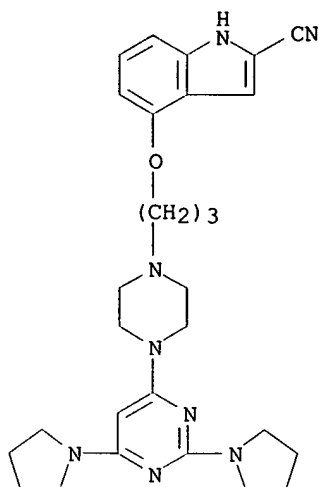
CN 1H-Indole-2-carboxamide, 4-[3-[4-(2,6-di-1-pyrrolidinyl-4-pyrimidinyl)-1-piperazinyl]propoxy]- (9CI) (CA INDEX NAME)



RN 145014-52-4 HCAPLUS
 CN 1H-Indole-2-carbonitrile, 4-[3-[4-(diphenylmethyl)-1-piperazinyl]propoxy]-
 (9CI) (CA INDEX NAME)



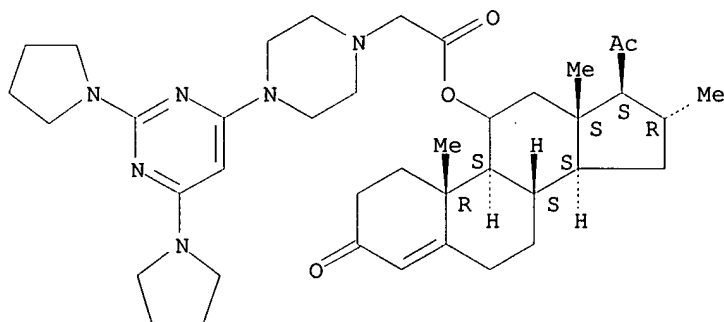
RN 145014-53-5 HCAPLUS
 CN 1H-Indole-2-carbonitrile, 4-[3-[4-(2,6-di-1-pyrrolidinyl-4-pyrimidinyl)-1-
 piperazinyl]propoxy]- (9CI) (CA INDEX NAME)



RN 145033-49-4 HCAPLUS

CN Pregn-4-ene-3,20-dione, 11-[[[4-(2,6-di-1-pyrrolidinyl-4-pyrimidinyl)-1-piperazinyl]acetyl]oxy]-16-methyl-, (16 α)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.

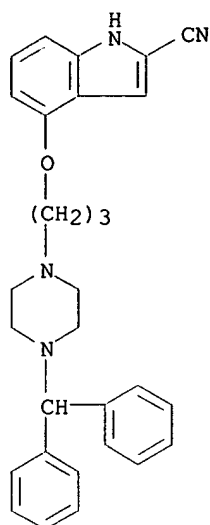


IT 145521-35-3P

RL: SPN (Synthetic preparation); PREP (Preparation)
(preparation of, for reversal of **multidrug** resistance to
neoplasm inhibitors)

RN 145521-35-3 HCAPLUS

CN 1H-Indole-2-carbonitrile, 4-[3-[4-(diphenylmethyl)-1-piperazinyl]propoxy]-
, dihydrochloride (9CI) (CA INDEX NAME)



● 2 HCl

L91 ANSWER 7 OF 11 HCAPLUS COPYRIGHT 2005 ACS on STN

ACCESSION NUMBER: 1989:463950 HCAPLUS

DOCUMENT NUMBER: 111:63950

TITLE: Topical pharmaceuticals containing triamcinolon
acetone-21-oic acid methyl ester for the prevention
of UV radiation-induced carcinogenic responses of the
skin

INVENTOR(S): Ross, Peter M.; Bradlow, Leon H.

PATENT ASSIGNEE(S): Rockefeller University, USA

SOURCE: PCT Int. Appl., 23 pp.

CODEN: PIXXD2

DOCUMENT TYPE: Patent

LANGUAGE: English

FAMILY ACC. NUM. COUNT: 2

PATENT INFORMATION:

| PATENT NO. | KIND | DATE | APPLICATION NO. | DATE |
|---|------|----------|-----------------|------------|
| WO 8807371 | A2 | 19881006 | WO 1988-US1036 | 19880325 |
| WO 8807371 | A3 | 19881201 | | |
| W: AU, JP | | | | |
| RW: AT, BE, CH, DE, FR, GB, IT, LU, NL, SE | | | | |
| AU 8817077 | A1 | 19881102 | AU 1988-17077 | 19880325 |
| AU 613370 | B2 | 19910801 | | |
| EP 307468 | A1 | 19890322 | EP 1988-904039 | 19880325 |
| R: AT, BE, CH, DE, FR, GB, IT, LI, LU, NL, SE | | | | |
| CA 1316827 | A1 | 19930427 | CA 1988-562419 | 19880325 |
| PRIORITY APPLN. INFO.: | | | | |
| | | | US 1987-30764 | A 19870325 |
| | | | US 1988-161542 | A 19880229 |
| | | | WO 1988-US1036 | A 19880325 |

AB Topical formulations containing triamcinolone acetone-21-oic acid Me ester (I), and, optionally, other compds., which inhibit prostaglandin biosynthesis through the arachidonic acid cascade, useful in the treatment of UV-exposed skin to inhibit UV radiation suppression of delayed hypersensitivity in the epidermis thereby reducing or obviating the carcinogenic effects of sunburn, are prepared A cream formulation contained I 0.5, cetyl esters wax 20.0, cetyl stearyl alc. 100.0, sorbitan monostearate 25.0, polysorbitan 60 20.0, cetyl dodecanol 100.0, propylene glycol 100.0, benzyl alc. 10.0 mg/g cream, and H₂O q.s. 1 g. The shaven lower backs of mice were exposed to 254 nm light at an incident dose of 12 W/cm² for 30-40 min (254 nm light penetrates the epidermis less deeply

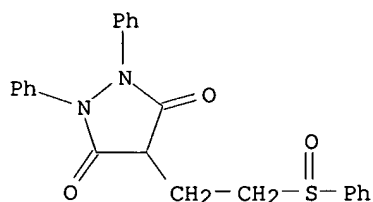
than UV light) and immediately following the irradiation treated with triamcinolone acetonide-21-oic acid methyl ester. This active agent had no effect on unirradiated skin but enhanced neutrophilic infiltration and epidermal hyperplasia in UV-irradiated skin. Alternatively, a method for the prevention of UV-induced carcinogenic effects comprises the administration of compds. affecting the arachidonic acid cascade or prostaglandin synthesis; such compds. are aspirin, ibuprofen, indomethacin, salicylic acid, phenylbutazone, sulfinpyrazon, and sulindac (no data).

IT 57-96-5, Sulfinpyrazon

RL: THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(**pharmaceuticals** containing, for prevention of UV-induced skin cancer)

RN 57-96-5 HCAPLUS

CN 3,5-Pyrazolidinedione, 1,2-diphenyl-4-[2-(phenylsulfinyl)ethyl]- (6CI, 7CI, 8CI, 9CI) (CA INDEX NAME)



L91 ANSWER 8 OF 11 HCAPLUS COPYRIGHT 2005 ACS on STN

ACCESSION NUMBER: 1986:61741 HCAPLUS

DOCUMENT NUMBER: 104:61741

TITLE: Mutagenicity and metabolic cooperation inhibition tests of cilostazol

AUTHOR(S): Shibahara, Toshikazu; Awogi, Takumi; Kaneko, Etsuko; Itoh, Toshiaki; Fukazawa, Yoko; Ishii, Kiyoshi; Tsushimoto, Gen

CORPORATE SOURCE: Tokushima Res. Inst., Otsuka Pharm. Co., Ltd., Tokushima, 771-01, Japan

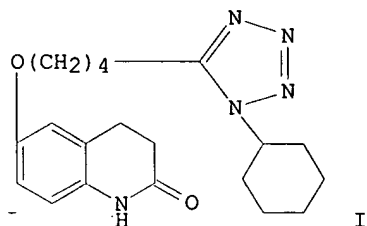
SOURCE: Iyakuin Kenkyu (1985), 16(5), 1093-9

CODEN: IYKEDH; ISSN: 0287-0894

DOCUMENT TYPE: Journal

LANGUAGE: Japanese

GI

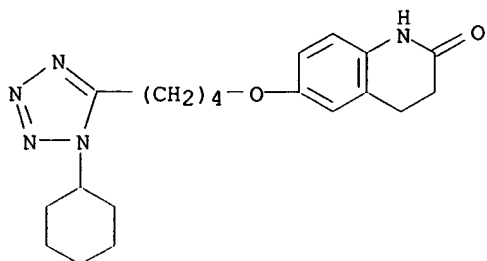


AB The antithrombotic **drug** cilostazol (I) [73963-72-1] was devoid of both mutagenicity (as measured by standard DNA-repair and reverse-mutation tests in bacteria) and of **tumor**-promoting activity (as measured by inhibition of metabolic cooperation between cultured Chinese hamster cells).

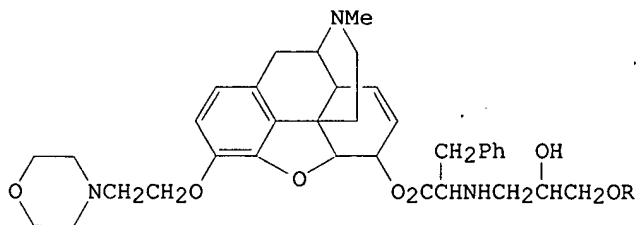
IT 73963-72-1

RL: BIOL (Biological study)
(mutagenicity of and **neoplasm** promotion by)

RN 73963-72-1 HCAPLUS
 CN 2(1H)-Quinolinone, 6-[4-(1-cyclohexyl-1H-tetrazol-5-yl)butoxy]-3,4-dihydro-
 (9CI) (CA INDEX NAME)



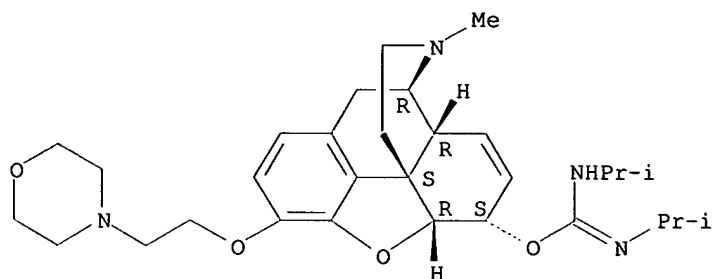
L91 ANSWER 9 OF 11 HCAPLUS COPYRIGHT 2005 ACS on STN
 ACCESSION NUMBER: 1983:221738 HCAPLUS
 DOCUMENT NUMBER: 98:221738
 TITLE: Fixation of drugs on cellulose releasable by enzymes
 AUTHOR(S): Lapique, Françoise; Dellacherie, Edith
 CORPORATE SOURCE: Lab. Chim. Phys. Macromol., ENSIC, Nancy, 54042, Fr.
 SOURCE: Makromolekulare Chemie (1983), 184(2), 277-85
 CODEN: MACEAK; ISSN: 0025-116X
 DOCUMENT TYPE: Journal
 LANGUAGE: French
 GI



AB As an approach to the programmed release of **drugs** a polymeric carrier (I; R = cellulose) from which the **drug** would be released by degradation of definite covalent chemical bonds by means of specific enzymes, pholcodine (II) [509-67-1], an **antitumor drug**, was coupled with an insol. physiol. inert polymer, cellulose [9004-34-6], using L-phenylalanine [63-91-2] as a spacer arm. An ester function was chosen linking the hydroxyl group of II and the carboxylic group of L-phenylalanine as the chemical bond between **drug** and amino acid. This linkage was not hydrolyzed in simulated digestive fluids containing pepsin or trypsin; it was only broken in the presence of α -chymotrypsin to slowly release the parent **drug**.

IT 85369-02-4P
 RL: RCT (Reactant); SPN (Synthetic preparation); PREP (Preparation); RACT (Reactant or reagent)
 (preparation and reaction with phenylalanine)
 RN 85369-02-4 HCAPLUS
 CN Morphinan-6-ol, 7,8-didehydro-4,5-epoxy-17-methyl-3-[2-(4-morpholinyl)ethoxy]-, N,N'-bis(1-methylethyl)carbamimidate (ester), (5 α ,6 α)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.

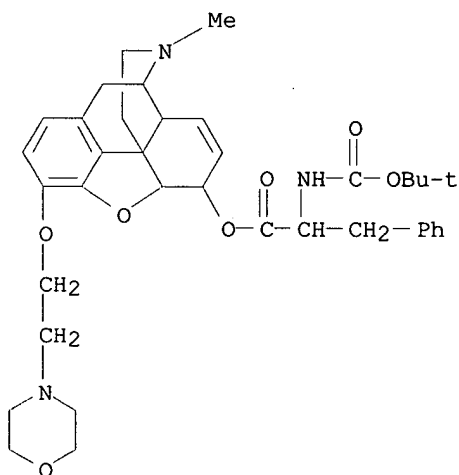


IT 85369-03-5P

RL: SPN (Synthetic preparation); PREP (Preparation)
(preparation of)

RN 85369-03-5 HCAPLUS

CN L-Phenylalanine, N-[(1,1-dimethylethoxy)carbonyl]-, (5 α ,6 α)-
7,8-didehydro-4,5-epoxy-17-methyl-3-[2-(4-morpholinyl)ethoxy]morphinan-6-
yl ester (9CI) (CA INDEX NAME)



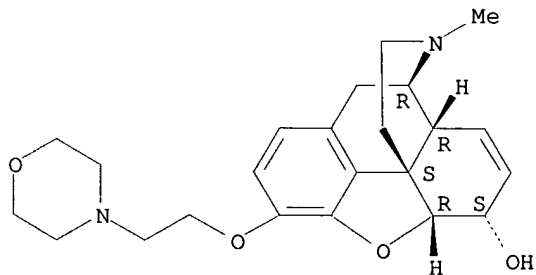
IT 509-67-1DP, reaction products with cellulose and phenylalanine

RL: SPN (Synthetic preparation); PREP (Preparation)
(preparation of, for **drug** release by enzyme cleavage)

RN 509-67-1 HCAPLUS

CN Morphinan-6-ol, 7,8-didehydro-4,5-epoxy-17-methyl-3-[2-(4-
morpholinyl)ethoxy]-, (5 α ,6 α)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



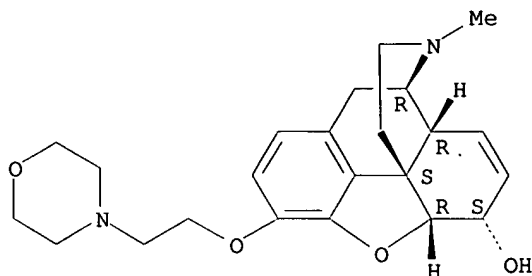
IT 509-67-1

RL: RCT (Reactant); RACT (Reactant or reagent)
(reaction of, with diisopropylcarbodiimide, isourea derivative from)

RN 509-67-1 HCAPLUS

CN Morphinan-6-ol, 7,8-didehydro-4,5-epoxy-17-methyl-3-[2-(4-morpholinyl)ethoxy]-, (5 α ,6 α)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



L91 ANSWER 10 OF 11 HCAPLUS COPYRIGHT 2005 ACS on STN

ACCESSION NUMBER: 1982:449486 HCAPLUS

DOCUMENT NUMBER: 97:49486

TITLE: Interruption of tumor-associated platelet consumption with platelet enzyme inhibitors

AUTHOR(S): Slichter, Sherrill J.; Weiden, Paul L.; O'Donnell, Margaret R.; Storb, Rainer

CORPORATE SOURCE: Sch. Med., Univ. Washington, Seattle, WA, 98104, USA

SOURCE: Blood (1982), 59(6), 1252-8

CODEN: BLOOAW; ISSN: 0006-4971

DOCUMENT TYPE: Journal

LANGUAGE: English

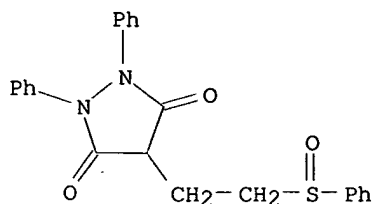
AB Twenty dogs with naturally occurring metastatic **tumors** were treated with anticoagulants (Warfarin [81-81-2]) or platelet enzyme inhibitor **drugs** (dipyridamole [58-32-2], dipyridamole plus aspirin [50-78-2], RA233 [13665-88-8], sulfinpyrazone [57-96-5], or a combination of RA233 and sulfinpyrazone) to determine if **tumor**-related redns. in platelet survival and concentration could be reversed. Anticoagulation was ineffective, while platelet enzyme inhibitors were able to produce improvements in platelet survival. Of the 18 dogs with metastatic **tumor** treated with platelet enzyme inhibitors, only 5 (28%) showed a reduction in platelet survival during the first week of observation on **therapy** compared to their baseline survivals. This is significantly different than the decreases in platelet survivals observed in 8 of 10 untreated dogs (80%) with metastatic **tumor** observed for the same interval. Furthermore, 8 of the 18 treated dogs (44%) had platelet survivals within 2 standard deviations of normal, compared to only 1 of 10 untreated dogs. Of the 8 dogs with normal platelet survivals, 6 were treated with a combination of a phosphodiesterase inhibitor (RA233 or dipyridamole) and a cyclooxygenase inhibitor (sulfinpyrazone or aspirin). The combination of RA233 and sulfinpyrazone was the best **drug** program tested and resulted in normal platelet survivals in 63% and improved platelet counts in 75% of the animals treated. Thus, platelet enzyme inhibitors with different mechanisms of action may have a synergistic effect in reversing the abnormal platelet hemostasis found in a variety of spontaneously occurring canine **neoplasms**.

IT 57-96-5

RL: BIOL (Biological study)
(platelet survival inhibition by **tumor** response to RA233 and)

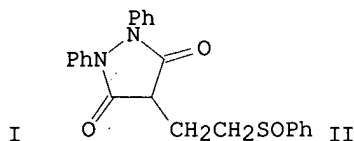
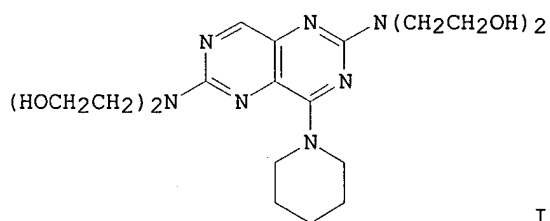
RN 57-96-5 HCAPLUS

CN 3,5-Pyrazolidinedione, 1,2-diphenyl-4-[2-(phenylsulfinyl)ethyl]- (6CI, 7CI, 8CI, 9CI) (CA INDEX NAME)



L91 ANSWER 11 OF 11 HCAPLUS COPYRIGHT 2005 ACS on STN
 ACCESSION NUMBER: 1981:52940 HCAPLUS
 DOCUMENT NUMBER: 94:52940
 TITLE: Antithrombotic pharmaceutical combination
 INVENTOR(S): Slichter, Sherrill J.
 PATENT ASSIGNEE(S): Thomae, Dr. Karl, G.m.b.H., Fed. Rep. Ger.
 SOURCE: Ger. Offen., 9 pp.
 CODEN: GWXXBX
 DOCUMENT TYPE: Patent
 LANGUAGE: German
 FAMILY ACC. NUM. COUNT: 1
 PATENT INFORMATION:

| PATENT NO. | KIND | DATE | APPLICATION NO. | DATE |
|---------------------------------------|------|----------|-----------------|------------|
| DE 2904736 | A1 | 19800828 | DE 1979-2904736 | 19790208 |
| US 4285945 | A | 19810825 | US 1979-76510 | 19790917 |
| EP 14392 | A1 | 19800820 | EP 1980-100385 | 19800125 |
| EP 14392 | B1 | 19811104 | | |
| R: BE, CH, DE, FR, GB, IT, LU, NL, SE | | | | |
| JP 55105618 | A2 | 19800813 | JP 1980-14258 | 19800207 |
| AU 8055311 | A1 | 19800814 | AU 1980-55311 | 19800207 |
| AU 533693 | B2 | 19831208 | | |
| ZA 8000715 | A | 19811028 | ZA 1980-715 | 19800207 |
| IL 59335 | A1 | 19830331 | IL 1980-59335 | 19800207 |
| PRIORITY APPLN. INFO.: GI | | | DE 1979-2904736 | A 19790208 |



AB A combination of I [13665-88-8] and sulfinpyrazone (II) [57-96-5] in a ratio of 10:1 to 1:10 is formulated in a sugar-coated tablet and capsule form for oral administration as an antithrombotic agent, the 2 components having a synergistic action in this respect. Thus, 50.0 mg I and 50.0 mg II were formulated into tablets. When dogs with malignant tumors were given the combination of I and II in a ratio of 1:1 or 1:2 in a dose of 50-100 mg/kg, the thrombocyte survival time in the body increased from .apprx.2 days to the near normal values of 4.5-4.8 days. The increase in the thrombocyte survival time (as measured with labeled cells) indicates a decreased tendency for thrombosis. The doses suggested for humans are 25-100 mg I and 50-175 mg II 2-4 times daily, and these are well below the LD50 levels.

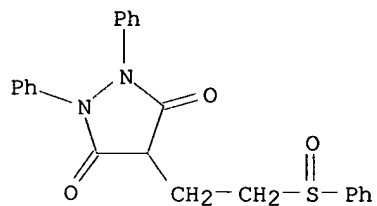
IT 57-96-5

RL: BIOL (Biological study)

(antithrombotic **pharmaceutical** synergistic combination with
piperidinopyrimidine derivative)

RN 57-96-5 HCAPLUS

CN 3,5-Pyrazolidinedione, 1,2-diphenyl-4-[2-(phenylsulfinyl)ethyl]- (6CI,
7CI, 8CI, 9CI) (CA INDEX NAME)



=>